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TRIAZOLE COMPOUNDS AND THEIR USE AS METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to a new class of compounds, to pharmaceutical compositions containing said compounds and to the use of said compounds in therapy. The present invention further relates to processes for the preparation of said compounds and to new intermediates used in the preparation thereof.

BACKGROUND OF THE INVENTION

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). Glutamate produces its effects on central neurons by binding to and thereby activating cell surface receptors. These receptors have been divided into two major classes, the ionotropic and metabotropic glutamate receptors, based on the structural features of the receptor proteins, the means by which the receptors transduce signals into the cell, and pharmacological profiles.

The metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors that activate a variety of intracellular second messenger systems following the binding of glutamate. Activation of mGluRs in intact mammalian neurons elicits one or more of the following responses: activation of phospholipase C; increases in phosphoinositide (PI) hydrolysis; intracellular calcium release; activation of phospholipase D; activation or inhibition of adenyl cyclase; increases or decreases in the formation of cyclic adenosine monophosphate (cAMP); activation of guanylyl cyclase; increases in the formation of cyclic guanosine monophosphate (cGMP); activation of phospholipase A_2; increases in arachidonic acid release; and increases or decreases in the activity of voltage- and ligand-gated ion channels. Schoepp *et al.*, *Trends Pharmacol. Sci. 14*:13 (1993), Schoepp, *Neurochem. Int. 24*:439 (1994), Pin *et al.*, *Neuropharmacology 34*:1 (1995), Bordi and Ugolini, *Prog. Neurobiol. 59*:55 (1999).

Eight distinct mGluR subtypes, termed mGluR1 through mGluR8, have been identified by molecular cloning. Nakanishi, *Neuron 13*:1031 (1994), Pin *et al.*, *Neuropharmacology 34*:1 (1995), Knopfel *et al.*, *J. Med. Chem. 38*:1417 (1995). Further receptor diversity occurs via expression of alternatively spliced forms of certain mGluR subtypes. Pin *et al.*,

PNAS 89:10331 (1992), Minakami *et al.*, *BBRC 199*:1136 (1994), Joly *et al.*, *J. Neurosci. 15*:3970 (1995).

Metabotropic glutamate receptor subtypes may be subdivided into three groups, Group I, Group II, and Group III mGluRs, based on amino acid sequence homology, the second messenger systems utilized by the receptors, and by their pharmacological characteristics. Group I mGluR comprises mGluR1, mGluR5 and their alternatively spliced variants. The binding of agonists to these receptors results in the activation of phospholipase C and the subsequent mobilization of intracellular calcium.

Neurological, psychiatric and pain disorders.

Attempts at elucidating the physiological roles of Group I mGluRs suggest that activation of these receptors elicits neuronal excitation. Various studies have demonstrated that Group I mGluRs agonists can produce postsynaptic excitation upon application to neurons in the hippocampus, cerebral cortex, cerebellum, and thalamus, as well as other CNS regions. Evidence indicates that this excitation is due to direct activation of postsynaptic mGluRs, but it also has been suggested that activation of presynaptic mGluRs occurs, resulting in increased neurotransmitter release. Baskys, *Trends Pharmacol. Sci. 15*:92 (1992), Schoepp, *Neurochem. Int. 24*:439 (1994), Pin *et al.*, *Neuropharmacology 34*:1(1995), Watkins *et al.*, *Trends Pharmacol. Sci. 15*:33 (1994).

Metabotropic glutamate receptors have been implicated in a number of normal processes in the mammalian CNS. Activation of mGluRs has been shown to be required for induction of hippocampal long-term potentiation and cerebellar long-term depression. Bashir *et al.*, *Nature 363*:347 (1993), Bortolotto *et al.*, *Nature 368*:740 (1994), Aiba *et al.*, *Cell 79*:365 (1994), Aiba *et al.*, *Cell 79*:377 (1994). A role for mGluR activation in nociception and analgesia also has been demonstrated. Meller *et al.*, *Neuroreport 4*: 879 (1993), Bordi and Ugolini, *Brain Res. 871*:223 (1999). In addition, mGluR activation has been suggested to play a modulatory role in a variety of other normal processes including synaptic transmission, neuronal development, apoptotic neuronal death, synaptic plasticity, spatial learning, olfactory memory, central control of cardiac activity, waking, motor control and control of the vestibulo-ocular reflex. Nakanishi, *Neuron 13*: 1031 (1994), Pin *et al.*, *Neuropharmacology 34*:1, Knopfel *et al.*, *J. Med. Chem. 38*:1417 (1995).

Further, Group I metabotropic glutamate receptors have been suggested to play roles in a variety of acute and chronic pathophysiological processes and disorders affecting the CNS. These include stroke, head trauma, anoxic and ischemic injuries, hypoglycemia, epilepsy,

neurodegenerative disorders such as Alzheimer's disease, psychiatric disorders and pain. Schoepp *et al.*, *Trends Pharmacol. Sci. 14*:13 (1993), Cunningham *et al.*, *Life Sci. 54*:135 (1994), Hollman *et al.*, *Ann. Rev. Neurosci. 17*:31 (1994), Pin *et al.*, *Neuropharmacology 34*:1 (1995), Knopfel *et al.*, *J. Med. Chem. 38*:1417 (1995), Spooren et al., *Trends Pharmacol. Sci. 22*:331 (2001), Gasparini et al. *Curr. Opin. Pharmacol. 2*:43 (2002), Neugebauer *Pain 98*:1 (2002). Much of the pathology in these conditions is thought to be due to excessive glutamate-induced excitation of CNS neurons. Because Group I mGluRs appear to increase glutamate-mediated neuronal excitation via postsynaptic mechanisms and enhanced presynaptic glutamate release, their activation probably contributes to the pathology. Accordingly, selective antagonists of Group I mGluR receptors could be therapeutically beneficial in all conditions underlain by excessive glutamate-induced excitation of CNS neurons, specifically as neuroprotective agents, analgesics or anticonvulsants.

Recent advances in the elucidation of the neurophysiological roles of metabotropic glutamate receptors generally and Group I in particular, have established these receptors as promising drug targets in the therapy of acute and chronic neurological and psychiatric disorders and chronic and acute pain disorders.

Gastro intestinal disorders

The lower esophageal sphincter (LES) is prone to relaxing intermittently. As a consequence, fluid from the stomach can pass into the esophagus since the mechanical barrier is temporarily lost at such times, an event hereinafter referred to as "G.I. reflux".

Gastro-esophageal reflux disease (GERD) is the most prevalent upper gastrointestinal tract disease. Current pharmacotherapy aims at reducing gastric acid secretion, or at neutralizing acid in the esophagus. The major mechanism behind G.I. reflux has been considered to depend on a hypotonic lower esophageal sphincter. However, e.g. *Holloway & Dent (1990) Gastroenterol. Clin. N. Amer. 19, pp. 517-535,* has shown that most reflux episodes occur during transient lower esophageal sphincter relaxations (TLESRs), i.e. relaxations not triggered by swallows. It has also been shown that gastric acid secretion usually is normal in patients with GERD.

The novel compounds according to the present invention are assumed to be useful for the inhibition of transient lower esophageal sphincter relaxations (TLESRs) and thus for treatment of gastro-esophageal reflux disorder (GERD).

The wording "TLESR", transient lower esophageal sphincter relaxations, is herein defined in accordance with *Mittal, R.K., Holloway, R.H., Penagini, R., Blackshaw, L.A., Dent, J., 1995; Transient lower esophageal sphincter relaxation. Gastroenterology 109, pp. 601-610.*

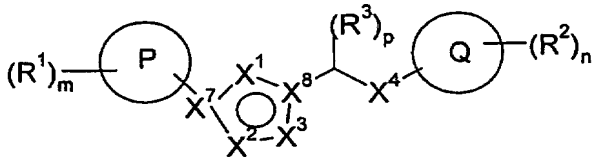
The wording "G.I. reflux" is herein defined as fluid from the stomach being able to pass into the esophagus, since the mechanical barrier is temporarily lost at such times.

The wording "GERD", gastro-esophageal reflux disease, is herein defined in accordance with *van Heerwarden, M.A., Smout A.J.P.M., 2000; Diagnosis of reflux disease. Baillière's Clin. Gastroenterol. 14, pp. 759-774.*

Because of their physiological and pathophysiological significance, there is a need for new potent mGluR agonists and antagonists that display a high selectivity for mGluR subtypes, particularly the Group I receptor subtype.

SUMMARY OF THE INVENTION

In one aspect of the invention there is provided a compound according to formula I



Formula I

wherein,

P is selected from aryl and heteroaryl

R^1 is attached to P via a carbon atom on ring P and is selected from the group consisting of hydrogen, hydroxy, halo, nitro, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{2-6}alkenyl, OC_{2-6}alkenyl, C_{2-6}alkynyl, OC_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, OC_{0-6}alkylC_{3-}

$_6$cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, CHO, $(CO)R^5$, $O(CO)R^5$, $O(CO)OR^5$, $O(CN)OR^5$, C_{1-6}alkylOR^5, OC_{2-6}alkylOR^5, C_{1-6}alkyl$(CO)R^5$, OC_{1-6}alkyl$(CO)R^5$, C_{0-6}alkylCO_2R^5, OC_{1-6}alkylCO_2R^5, C_{0-6}alkylcyano, OC_{2-6}alkylcyano, C_{0-6}alkylNR^5R^6, OC_{2-6}alkylNR^5R^6, C_{1-6}alkyl$(CO)NR^5R^6$, OC_{1-6}alkyl$(CO)NR^5R^6$, C_{0-6}alkyl$NR^5(CO)R^6$, OC_{2-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)NR^5R^6$, C_{0-6}alkylSR^5, OC_{2-6}alkylSR^5, C_{0-6}alkyl$(SO)R^5$, OC_{2-6}alkyl$(SO)R^5$, C_{0-6}alkylSO_2R^5, OC_{2-6}alkylSO_2R^5, C_{0-6}alkyl$(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)NR^5R^6$, C_{0-6}alkyl$NR^5(SO_2)R^6$, OC_{2-6}alkyl$NR^5(SO_2)R^6$, C_{0-6}alkyl$NR^5(SO_2)NR^5R^6$, OC_{2-6}alkyl$NR^5(SO_2)NR^5R^6$, $(CO)NR^5R^6$, $O(CO)NR^5R^6$, NR^5OR^6, C_{0-6}alkyl$NR^5(CO)OR^6$, OC_{2-6}alkyl$NR^5(CO)OR^6$, SO_3R^5 and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S;

R^5 and R^6 are independently selected from a group consisting of hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl and aryl;

X^1, X^2, and X^3, are independently selected from the group consisting of CR^4, N, O and S;

wherein at least one of X^1, X^2, and X^3 is not N;

X^7 and X^8 are selected from the group consisting of C and N such that when X^7 is N, X^8 is C and when X^7 is C, X^8 is N;

R^4 is selected from the group consisting of H, =O, C_{1-6}alkyl, OH;

X^4 is selected from the group consisting of CR^7R^8, NR^7, O, S, SO, and SO_2;

R^7 and R^8 are independently selected from a group consisting of hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl and aryl;

R^3 is selected from the group consisting of H, C_{1-6}alkyl, hydroxy, C_{0-6}alkylcyano, oxo, $=NR^5$, $=NOR^5$, C_{1-4}alkylhalo, halo, C3-7cycloalkyl, $O(CO)C_{1-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-4}alkyl$(SO_2)C_{0-4}$alkyl, $(SO)C_{0-4}$alkyl, $(SO_2)C_{0-4}$alkyl, OC_{1-4}alkyl, C_{1-4}alkylOR^5 and C_{0-4}alkylNR^5R^6;

R^3 can optionally bond to the ring Q to form a fused cyclic group;

R^7 or R^8 can optionally bond to R^3 or to the ring Q to form a cyclic or a fused cyclic group respectively;

ring Q has 5- to 7-members and may be cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^2 is selected from the group consisting of hydroxy, C_{0-6}alkylcyano, $=NR^5$, $=NOR^5$, C_{1-4}alkylhalo, halo, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylcycloalkyl, C_{0-6}alkylheterocycloalkyl, OC_{1-4}alkyl, OC_{0-6}alkylaryl, $O(CO)C_{1-4}$alkyl, $(CO)OC_{1-4}$alkyl, C_{0-4}alkyl$(S)C_{0-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-4}alkyl$(SO_2)C_{0-4}$alkyl, $(SO)C_{0-4}$alkyl, $(SO_2)C_{0-4}$alkyl, C_{1-4}alkylOR^5, C_{0-}

$_4$alkylNR^{5}R^6 and a 5- or 6-membered ring containing atoms independently selected from C, N, O and S, which ring may optionally be fused with a 5- or 6-membered ring containing one or more atoms independently selected from the group consisting of C, N and O and wherein said ring and said fused ring may be substituted by one or more A;

wherein any C_{1-6}alkyl, aryl or heteroaryl defined under R^1, R^2 and R^3 may be substituted by one or more A ;

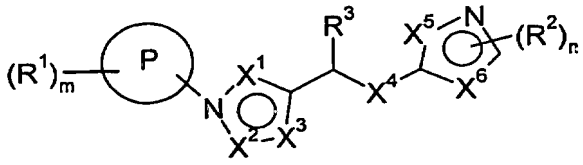
A is selected from the group consisting of hydrogen, hydroxy, halo, nitro, oxo, C_{0-6}alkylcyano, C_{0-4}alkylC_{3-6}cycloalkyl, C_{1-6}alkyl, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{2-6}alkenyl, C_{0-3}alkylaryl, C_{0-6}alkylOR^5, OC_{2-6}alkylOR^5, C_{1-6}alkylSR^5, OC_{2-6}alkylSR^5, $(CO)R^5$, $O(CO)R^5$, OC_{2-6}alkylcyano, OC_{1-6}alkylCO_2R^5, $O(CO)OR^5$, OC_{1-6}alkyl$(CO)R^5$, C_{1-6}alkyl$(CO)R^5$, NR^5OR^6, C_{1-6}alkylNR^5R^6, OC_{2-6}alkylNR^5R^6, C_{0-6}alkyl$(CO)NR^5R^6$, OC_{1-6}alkyl$(CO)NR^5R^6$, OC_{2-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)NR^5R^6$, $O(CO)NR^5R^6$, C_{0-6}alkyl$(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)NR^5R^6$, C_{0-6}alkyl$NR^5(SO_2)R^6$, OC_{2-6}alkyl$NR^5(SO_2)R^6$, SO_3R^5, C_{1-6}alkyl$NR^5(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)R^5$, C_{0-6}alkyl$(SO_2)R^5$, C_{0-6}alkyl$(SO)R^5$, OC_{2-6}alkyl$(SO)R^5$ and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S;

m is selected from 0, 1, 2, 3 and 4;

n is selected from 0, 1, 2, 3 and 4; and

a salt or hydrate thereof.

In another aspect of the invention there is provided a compound of Formula II



Formula II

wherein,

P is selected from aryl and heteroaryl;

R^1 is attached to P via a carbon atom on ring P and is selected from the group consisting of hydrogen, hydroxy, halo, nitro, C_{1-5}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{2-6}alkenyl, OC_{2-6}alkenyl, C_{2-6}alkynyl, OC_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, OC_{0-6}alkylC_{3-}

$_{6}$cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, CHO, $(CO)R^5$, $O(CO)R^5$, $O(CO)OR^5$, $O(CN)OR^5$, C_{1-6}alkylOR^5, OC_{2-6}alkylOR^5, C_{1-6}alkyl$(CO)R^5$, OC_{1-6}alkyl$(CO)R^5$, C_{0-6}alkylCO_2R^5, OC_{1-6}alkylCO_2R^5, C_{0-6}alkylcyano, OC_{2-6}alkylcyano, C_{0-6}alkylNR^5R^6, OC_{2-6}alkylNR^5R^6, C_{1-6}alkyl$(CO)NR^5R^6$, OC_{1-6}alkyl$(CO)NR^5R^6$, C_{0-6}alkyl$NR^5(CO)R^6$, OC_{2-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)NR^5R^6$, C_{0-6}alkylSR^5, OC_{2-6}alkylSR^5, C_{0-6}alkyl$(SO)R^5$, OC_{2-6}alkyl$(SO)R^5$, C_{0-6}alkylSO_2R^5, OC_{2-6}alkylSO_2R^5, C_{0-6}alkyl$(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)NR^5R^6$,C_{0-6}alkyl$NR^5(SO_2)R^6$, OC_{2-6}alkyl$NR^5(SO_2)R^6$, C_{0-6}alkyl$NR^5(SO_2)NR^5R^6$, OC_{2-6}alkyl$NR^5(SO_2)NR^5R^6$, $(CO)NR^5R^6$, $O(CO)NR^5R^6$, NR^5OR^6, C_{0-6}alkyl$NR^5(CO)OR^6$, OC_{2-6}alkyl$NR^5(CO)OR^6$, SO_3R^5 and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S;

R^5 and R^6 are independently selected from a group consisting of hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl and aryl;

X^1 and X^2 are independently selected from the group consisting of CR^4, and N;

X^3 is selected from the group consisting of CR^4, N, and O; wherein at least one of X^1 X^2 and X^3 is not N;

R^4 is selected from the group consisting of H, =O, C_{1-6}alkyl, OH;

R^3 is selected from the group consisting of H, C_{1-6}alkyl, hydroxy, C_{0-6}alkylcyano, oxo, $=NR^5$, $=NOR^5$, C_{1-4}alkylhalo, halo, C3-7cycloalkyl, $O(CO)C_{1-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-4}alkyl$(SO_2)C_{0-4}$alkyl, $(SO)C_{0-4}$alkyl, $(SO_2)C_{0-4}$alkyl, OC_{1-4}alkyl, C_{1-4}alkylOR^5 and C_{0-4}alkylNR^5R^6;

X^4 is selected from the group consisting of CR^7R^8, NR^7, O, S, SO, and SO_2;

R^7 and R^8 are independently selected from a group consisting of hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl and aryl;

X^5 and X^6 are independently selected from the group consisting of C, N, O and S;

R^2 is selected from the group consisting of hydroxy, C_{0-6}alkylcyano, $=NR^5$, $=NOR^5$, C_{1-4}alkylhalo, halo, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylcycloalkyl, C_{0-6}alkylheterocycloalkyl, OC_{1-4}alkyl, OC_{0-6}alkylaryl, $O(CO)C_{1-4}$alkyl, $(CO)OC_{1-4}$alkyl, C_{0-4}alkyl$(S)C_{0-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-4}alkyl$(SO_2)C_{0-4}$alkyl, $(SO)C_{0-4}$alkyl, $(SO_2)C_{0-4}$alkyl, C_{1-4}alkylOR^5, C_{0-4}alkylNR^5R^6 and a 5- or 6-membered ring containing atoms independently selected from C, N, O and S, and wherein said ring may be substituted by one or more A; and

any C_{1-6}alkyl, aryl or heteroaryl defined under R^1, R^2 and R^3 may be substituted by one or more A;

A is selected from the group consisting of hydrogen, hydroxy, halo, nitro, oxo, C_{0-6}alkylcyano, C_{0-4}alkylC_{3-6}cycloalkyl, C_{1-6}alkyl, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{2-6}alkenyl, C_{0-3}alkylaryl, C_{0-6}alkylOR^5, OC_{2-6}alkylOR^5, C_{1-6}alkylSR^5, OC_{2-6}alkylSR^5, $(CO)R^5$, $O(CO)R^5$, OC_{2-6}alkylcyano, OC_{1-6}alkylCO_2R^5, $O(CO)OR^5$, OC_{1-6}alkyl$(CO)R^5$, C_{1-6}alkyl$(CO)R^5$, NR^5OR^6, C_{1-6}alkylNR^5R^6, OC_{2-6}alkylNR^5R^6, C_{0-6}alkyl$(CO)NR^5R^6$, OC_{1-6}alkyl$(CO)NR^5R^6$, OC_{2-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)NR^5R^6$, $O(CO)NR^5R^6$, C_{0-6}alkyl$(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)NR^5R^6$, C_{0-6}alkyl$NR^5(SO_2)R^6$, OC_{2-6}alkyl$NR^5(SO_2)R^6$, SO_3R^5, C_{1-6}alkyl$NR^5(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)R^5$, C_{0-6}alkyl$(SO_2)R^5$, C_{0-6}alkyl$(SO)R^5$, OC_{2-6}alkyl$(SO)R^5$ and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S;

m is selected from 0, 1, 2, 3 and 4;

n is selected from 0, 1, 2, 3 and 4;

p is selected from 1 and 2; and

a salts or hydrates thereof ,

In a further aspect of the invention there is provided pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I or formula II and a pharmaceutically acceptable diluent, excipients and/or inert carrier.

In yet a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula I, or formula II for use in the treatment of mGluR5 receptor mediated disorders, and for use in the treatment of neurological disorders, psychiatric disorders, gastrointestinal disorders and pain disorders.

In still a further aspect of the invention there is provided the compound of formula I or formula II for use in therapy, especially for the treatment of mGluR5 receptor mediated disorders, and for the treatment of neurological disorders, psychiatric disorders, gastrointestinal disorders and pain disorders.

In another aspect of the invention there is provided processes for the preparation of compounds of formula I and formula II and the intermediates used in the preparation thereof.

A further aspect of the invention is the use of a compound according to formula I for the manufacture of a medicament for the treatment or prevention of obesity and obesity related conditions, as well as treating eating disorders by inhibition of excessive food intake and the resulting obesity and complications associated therewith.

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These and other aspects of the present invention are described in greater detail herein below.

DETAILED DESCRIPTION OF THE INVENTION

The object of the present invention is to provide compounds exhibiting an activity at metabotropic glutamate receptors (mGluRs), especially at the mGluR5 receptors.

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-6}' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms. Similarly 'C_{1-3}' means a carbon group having 1, 2, or 3 carbon atoms

In the case where a subscript is the integer 0 (zero) the group to which the subscript refers indicates that the group is absent.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl, t-hexyl. The term C_{1-3}alkyl has 1 to 3 carbon atoms and may be methyl, ethyl, n-propyl or i-propyl.

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring system. The term "C_{3-7}cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

In this specification, unless stated otherwise, the term "alkoxy" includes both straight or branched alkoxy groups. C_{1-3}alkoxy may be, but is not limited to methoxy, ethoxy, n-propoxy or i-propoxy.

In this specification, unless stated otherwise, the term "bond" may be a saturated or unsaturated bond.

In this specification, unless stated otherwise, the term "halo" and "halogen" may be fluoro, chloro, bromo or iodo.

In this specification, unless stated otherwise, the term "alkylhalo" means an alkyl group as defined above, which is substituted with halo as described above. The term "C_{1-6}alkylhalo" may include, but is not limited to fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl or bromopropyl. The term "OC_{1-6}alkylhalo" may include, but is not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy or difluoroethoxy.

In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl groups. The term "C_{2-6}alkenyl" refers to an alkenyl group having 2 to 6 carbon atoms and one or two double bonds, and may be, but is not limited to vinyl, allyl, propenyl, i-propenyl, butenyl, i-butenyl, crotyl, pentenyl, i-pentenyl and hexenyl.

In this specification, unless stated otherwise, the term "alkynyl" includes both straight and branched chain alkynyl groups. The term C_{2-6}alkynyl having 2 to 6 carbon atoms and one or two triple bonds, and may be, but is not limited to ethynyl, propargyl, butynyl, i-butynyl, pentynyl, i-pentynyl and hexynyl.

In this specification unless otherwise stated the term "aryl" refers to an optionally substituted monocyclic or bicyclic hydrocarbon ring system containing at least one unsaturated aromatic ring. Examples and suitable values of the term "aryl" are phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indyl and indenyl.

In this specification, unless stated otherwise, the term "heteroaryl" refers to an optionally substituted monocyclic or bicyclic unsaturated, ring system containing at least one heteroatom selected independently from N, O or S. Examples of "heteroaryl" may be, but are not limited to thiophene, thienyl, pyridyl, thiazolyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxadiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolonyl, oxazolonyl,

thiazolonyl, tetrazolyl and thiadiazolyl, benzoimidazolyl, benzooxazolyl, tetrahydrotriazolopyridyl, tetrahydrotriazolopyrimidinyl, benzofuryl, indolyl, isoindolyl, pyridonyl, pyridazinyl, pyrimidinyl, imidazopyridyl, oxazolopyridyl, thiazolopyridyl, pyridyl, imidazopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl and purinyl.

In this specification, unless stated otherwise, the term "alkylaryl", "alkylheteroaryl " and "alkylcycloalkyl " refer to a substituent that is attached via the alkyl group to an aryl, heteroaryl and cycloalkyl group.

In this specification, unless stated otherwise, the term "heterocycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring system wherein one or more of the carbon atoms are replaced with heteroatom. The term "heterocycloalkyl" includes but is not limited to pyrrolidine, tetrahydrofuran, tetrahydrothiophene, piperidine, piperazine, morpholine, thiomorpholine, tetrahydropyran, tetrahydrothiopyran.

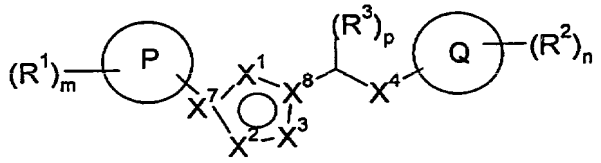
In this specification, unless stated otherwise the term "5- or 6-membered ring containing atoms independently selected from C, N, O or S", includes aromatic and heteroaromatic rings as well as carbocyclic and heterocyclic rings, which may be saturated partially saturated or unsaturated. Examples of such rings may be, but are not limited to furyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, thienyl, imidazolyl, imidazolidinyl, imidazolinyl, triazolyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, thiomorpholinyl, phenyl, cyclohexyl, cyclopentyl and cyclohexenyl.

In this specification, unless stated otherwise, the term "$=NR^5$" and "$=NOR^5$" include imino- and oximo- groups carrying an R^5 substituent and may be, or be part of, groups including, but not limited to iminoalkyl, iminohydroxy, iminoalkoxy, amidine, hydroxyamidine and alkoxyamidine.

In the case where a subscript is the integer 0 (zero) the group to which the subscript refers, indicates that the group is absent, i.e. there is a direct bond between the groups.
In this specification unless stated otherwise the term "fused rings" refers to two rings which share 2 common atoms.

In this specification, unless stated otherwise, the term "bridge" means a molecular fragment, containing one or more atoms, or a bond, which connects two remote atoms in a ring, thus forming either bi- or tricyclic systems.

One embodiment of the invention relates to compounds of Formula I



Formula I

wherein,

P is selected from aryl and heteroaryl

R^1 is attached to P via a carbon atom on ring P and is selected from the group consisting of hydrogen, hydroxy, halo, nitro, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{2-6}alkenyl, OC_{2-6}alkenyl, C_{2-6}alkynyl, OC_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, OC_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, CHO, $(CO)R^5$, $O(CO)R^5$, $O(CO)OR^5$, $O(CN)OR^5$, C_{1-6}alkylOR^5, OC_{2-6}alkylOR^5, C_{1-6}alkyl$(CO)R^5$, OC_{1-6}alkyl$(CO)R^5$, C_{0-6}alkylCO_2R^5, OC_{1-6}alkylCO_2R^5, C_{0-6}alkylcyano, OC_{2-6}alkylcyano, C_{0-6}alkylNR^5R^6, OC_{2-6}alkylNR^5R^6, C_{1-6}alkyl$(CO)NR^5R^6$, OC_{1-6}alkyl$(CO)NR^5R^6$, C_{0-6}alkyl$NR^5(CO)R^6$, OC_{2-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)NR^5R^6$, C_{0-6}alkylSR^5, OC_{2-6}alkylSR^5, C_{0-6}alkyl$(SO)R^5$, OC_{2-6}alkyl$(SO)R^5$, C_{0-6}alkylSO_2R^5, OC_{2-6}alkylSO_2R^5, C_{0-6}alkyl$(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)NR^5R^6$,C_{0-6}alkyl$NR^5(SO_2)R^6$, OC_{2-6}alkyl$NR^5(SO_2)R^6$, C_{0-6}alkyl$NR^5(SO_2)NR^5R^6$, OC_{2-6}alkyl$NR^5(SO_2)NR^5R^6$, $(CO)NR^5R^6$, $O(CO)NR^5R^6$, NR^5OR^6, C_{0-6}alkyl$NR^5(CO)OR^6$, OC_{2-6}alkyl$NR^5(CO)OR^6$, SO_3R^5 and a 5- or 6-membered ring containing one or more atoms independently selected from the group consisting of C, N, O and S;

R^5 and R^6 are independently selected from a group consisting of hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl and aryl;

X^1, X^2, and X^3, are independently selected from the group consisting of CR^4, N, O and S; wherein at least one of X^1, X^2, and X^3 is not N;

X^7 and X^8 are selected from the group consisting of C and N such that when X^7 is N, X^8 is C and when X^7 is C, X^8 is N;

R^4 is selected from the group consisting of H, =O, C_{1-6}alkyl, OH;

X^4 is selected from the group consisting of CR^7R^8, NR^7, O, S, SO, and SO_2;

R^7 and R^8 are independently selected from a group consisting of hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl and aryl;

R^3 is selected from the group consisting of H, C_{1-6}alkyl, hydroxy, C_{0-6}alkylcyano, oxo, $=NR^5$, $=NOR^5$, C_{1-4}alkylhalo, halo, C3-7cycloalkyl, $O(CO)C_{1-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-4}alkyl$(SO_2)C_{0-4}$alkyl, $(SO)C_{0-4}$alkyl, $(SO_2)C_{0-4}$alkyl, OC_{1-4}alkyl, C_{1-4}alkylOR^5 and C_{0-4}alkylNR^5R^6;

R^3 can optionally bond to the ring Q to form a fused cyclic group;

R^7 or R^8 can optionally bond to R^3 or to the ring Q to form a cyclic or a fused cyclic group respectively;

ring Q has 5- to 7-members and may be carbocyclic, heterocyclic, aryl heteroaryl;

R^2 is selected from the group consisting of hydroxy, C_{0-6}alkylcyano, $=NR^5$, $=NOR^5$, C_{1-4}alkylhalo, halo, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylcycloalkyl, C_{0-6}alkylheterocycloalkyl, OC_{1-4}alkyl, OC_{0-6}alkylaryl, $O(CO)C_{1-4}$alkyl, $(CO)OC_{1-4}$alkyl, C_{0-4}alkyl$(S)C_{0-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-4}alkyl$(SO_2)C_{0-4}$alkyl, $(SO)C_{0-4}$alkyl, $(SO_2)C_{0-4}$alkyl, C_{1-4}alkylOR^5, C_{0-4}alkylNR^5R^6 and a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O and S, which ring may optionally be fused with a 5- or 6-membered ring containing one or more atoms independently selected from the group consisting of C, N and O and wherein said ring and said fused ring may be substituted by one or more A;

wherein any C_{1-6}alkyl, aryl or heteroaryl defined under R^1, R^2 and R^3 may be substituted by one or more A ;

A is selected from the group consisting of hydrogen, hydroxy, halo, nitro, oxo, C_{0-6}alkylcyano, C_{0-4}alkylC_{3-6}cycloalkyl, C_{1-6}alkyl, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{2-6}alkenyl, C_{0-3}alkylaryl, C_{0-6}alkylOR^5, OC_{2-6}alkylOR^5, C_{1-6}alkylSR^5, OC_{2-6}alkylSR^5, $(CO)R^5$, $O(CO)R^5$, OC_{2-6}alkylcyano, OC_{1-6}alkylCO_2R^5, $O(CO)OR^5$, OC_{1-6}alkyl$(CO)R^5$, C_{1-6}alkyl$(CO)R^5$, NR^5OR^6, C_{1-6}alkylNR^5R^6, OC_{2-6}alkylNR^5R^6, C_{0-6}alkyl$(CO)NR^5R^6$, OC_{1-6}alkyl$(CO)NR^5R^6$, OC_{2-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)NR^5R^6$, $O(CO)NR^5R^6$, C_{0-6}alkyl$(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)NR^5R^6$, C_{0-6}alkyl$NR^5(SO_2)R^6$, OC_{2-6}alkyl$NR^5(SO_2)R^6$, SO_3R^5, C_{1-6}alkyl$NR^5(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)R^5$, C_{0-6}alkyl$(SO_2)R^5$, C_{0-6}alkyl$(SO)R^5$, OC_{2-6}alkyl$(SO)R^5$ and a 5- or 6-

membered ring containing one or more atoms independently selected from the group consisting of C, N, O and S;

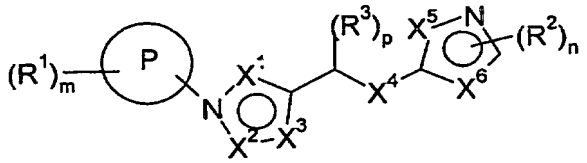
m is selected from 0, 1, 2, 3 and 4;

n is selected from 0, 1, 2, 3 and 4;

p is selected from 1 and 2; and

a salt or hydrate thereof.

Another embodiment of the invention relates to compounds of Formula II



Formula II

wherein,

P is selected from aryl and heteroaryl;

R^1 is attached to P via a carbon atom on ring P and is selected from the group consisting of hydrogen, hydroxy, halo, nitro, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{2-6}alkenyl, OC_{2-6}alkenyl, C_{2-6}alkynyl, OC_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, OC_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, CHO, $(CO)R^5$, $O(CO)R^5$, $O(CO)OR^5$, $O(CN)OR^5$, C_{1-6}alkylOR^5, OC_{2-6}alkylOR^5, C_{1-6}alkyl$(CO)R^5$, OC_{1-6}alkyl$(CO)R^5$, C_{0-6}alkylCO_2R^5, OC_{1-6}alkylCO_2R^5, C_{0-6}alkylcyano, OC_{2-6}alkylcyano, C_{0-6}alkylNR^5R^6, OC_{2-6}alkylNR^5R^6, C_{1-6}alkyl$(CO)NR^5R^6$, OC_{1-6}alkyl$(CO)NR^5R^6$, C_{0-6}alkyl$NR^5(CO)R^6$, OC_{2-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)NR^5R^6$, C_{0-6}alkylSR^5, OC_{2-6}alkylSR^5, C_{0-6}alkyl$(SO)R^5$, OC_{2-6}alkyl$(SO)R^5$, C_{0-6}alkylSO_2R^5, OC_{2-6}alkylSO_2R^5, C_{0-6}alkyl$(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)NR^5R^6$,C_{0-6}alkyl$NR^5(SO_2)R^6$, OC_{2-6}alkyl$NR^5(SO_2)R^6$, C_{0-6}alkyl$NR^5(SO_2)NR^5R^6$, OC_{2-6}alkyl$NR^5(SO_2)NR^5R^6$, $(CO)NR^5R^6$, $O(CO)NR^5R^6$, NR^5OR^6, C_{0-6}alkyl$NR^5(CO)OR^6$, OC_{2-6}alkyl$NR^5(CO)OR^6$, SO_3R^5 and a 5- or 6-membered ring containing one or more atoms independently selected from the group consisting of C, N, O and S;

R^5 and R^6 are independently selected from a group consisting of hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl and aryl;

X^1 and X^2 are independently selected from the group consisting of CR^4, and N;

X^3 is selected from the group consisting of CR^4, N, and O; wherein at least one of X^1 X^2 and X^3 is not N;

R^4 is selected from the group consisting of H, =O, C_{1-6}alkyl, OH;

R^3 is selected from the group consisting of H, C_{1-6}alkyl, hydroxy, C_{0-6}alkylcyano, oxo, $=NR^5$, $=NOR^5$, C_{1-4}alkylhalo, halo, C3-7cycloalkyl, $O(CO)C_{1-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-4}alkyl$(SO_2)C_{0-4}$alkyl, $(SO)C_{0-4}$alkyl, $(SO_2)C_{0-4}$alkyl, OC_{1-4}alkyl, C_{1-4}alkylOR^5 and C_{0-4}alkylNR^5R^6;

X^4 is selected from the group consisting of CR^7R^8, NR^7, O, S, SO, and SO_2;

R^7 and R^8 are independently selected from a group consisting of hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl and aryl;

X^5 and X^6 are independently selected from the group consisting of C, N, O and S;

R^2 is selected from the group consisting of hydrogen, hydroxy, C_{0-6}alkylcyano, $=NR^5$, $=NOR^5$, C_{1-4}alkylhalo, halo, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylcycloalkyl, C_{0-6}alkylheterocycloalkyl, OC_{1-4}alkyl, OC_{0-6}alkylaryl, $O(CO)C_{1-4}$alkyl, $(CO)OC_{1-4}$alkyl, C_{0-4}alkyl$(S)C_{0-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-4}alkyl$(SO_2)C_{0-4}$alkyl, $(SO)C_{0-4}$alkyl, $(SO_2)C_{0-4}$alkyl, C_{1-4}alkylOR^5, C_{0-4}alkylNR^5R^6 and a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O and S, and wherein said ring may be substituted by one or more A; and

any C_{1-6}alkyl, aryl or heteroaryl defined under R^1, R^2 and R^3 may be substituted by one or more A;

A is selected from the group consisting of hydrogen, hydroxy, halo, nitro, oxo, C_{0-6}alkylcyano, C_{0-4}alkylC_{3-6}cycloalkyl, C_{1-6}alkyl, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{2-6}alkenyl, C_{0-3}alkylaryl, C_{0-6}alkylOR^5, OC_{2-6}alkylOR^5, C_{1-6}alkylSR^5, OC_{2-6}alkylSR^5, $(CO)R^5$, $O(CO)R^5$, OC_{2-6}alkylcyano, OC_{1-6}alkylCO_2R^5, $O(CO)OR^5$, OC_{1-6}alkyl$(CO)R^5$, C_{1-6}alkyl$(CO)R^5$, NR^5OR^6, C_{1-6}alkylNR^5R^6, OC_{2-6}alkylNR^5R^6, C_{0-6}alkyl$(CO)NR^5R^6$, OC_{1-6}alkyl$(CO)NR^5R^6$, OC_{2-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)NR^5R^6$, $O(CO)NR^5R^6$, C_{0-6}alkyl$(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)NR^5R^6$, C_{0-6}alkyl$NR^5(SO_2)R^6$, OC_{2-6}alkyl$NR^5(SO_2)R^6$, SO_3R^5, C_{1-6}alkyl$NR^5(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)R^5$, C_{0-6}alkyl$(SO_2)R^5$, C_{0-6}alkyl$(SO)R^5$, OC_{2-6}alkyl$(SO)R^5$ and a 5- or 6-membered ring containing one or more atoms independently selected from the group consisting of C, N, O and S;

m is selected from 0, 1, 2, 3 and 4;

n is selected from 0, 1, 2, 3 and 4;

p is selected from 1 and 2; and

and a salts or hydrates thereof ,

Another embodiment the invention relates to the compounds:

3-(3-chlorophenyl)-5-{[(4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)thio]methyl}-1,3,4-oxadiazol-2(3H)-one

2-(3-chlorophenyl)-5-{1-[methyl(4-methyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl)amino]ethyl}-2,4-dihydro-3H-1,2,4-triazol-3-one

4-(5-{1-[1-(3-chlorophenyl)-1H-pyrazol-4-yl]ethoxy}-4-methyl-4H-1,2,4-triazol-3-yl)pyridine

4-(5-{1-[2-(3-chlorophenyl)-2H-1,2,3-triazol-4-yl]ethoxy}-4-methyl-4H-1,2,4-triazol-3-yl)pyridine

4-[5-({1-[2-(3-chlorophenyl)-2H-1,2,3-triazol-4-yl]ethyl}thio)-4-cyclopropyl-4H-1,2,4-triazol-3-yl]pyridine

4-{5-[1-(3-Chloro-phenyl)-1H-[1,2,4]triazol-3-ylmethylsulfanyl]-4-cyclopropyl-4H-[1,2,4]triazol-3-yl}-pyridine

4-{5-[1-(3-Chloro-phenyl)-1H-[1,2,4]triazol-3-ylmethoxy]-4-cyclopropyl-4H-[1,2,4]triazol-3-yl}-pyridine

4-{5-[1-(3-Chloro-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-4-methyl-4H-[1,2,4]triazol-3-yl}-pyridine

4-{5-[1-(3-Chloro-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-4-cyclopropyl-4H-[1,2,4]triazol-3-yl}-pyridine

4-{5-[1-(3-Chloro-phenyl)-1H-[1,2,3]triazol-4-ylmethoxy]-4-cyclopropyl-4H-[1,2,4]triazol-3-yl}-pyridine and

4-(5-{(1*R*)-[2-(3-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]ethoxy}-4-methyl-4*H*-1,2,4-triazol-3-yl)pyridine

or a salt or hydrate thereof.

This invention relates to triazoles and other heterocyclic compounds of formulas I and II, having a variable P. In one embodiment of the invention P is selected from aryl and heteroaryl. In another embodiment P is aryl and in still another embodiment P is phenyl.

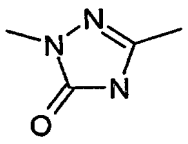
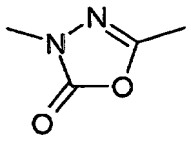
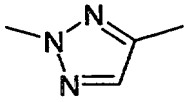
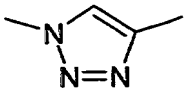
According to Formulas I and II, P can be substituted with 0 to 4 substituents R^1. In one embodiment of the invention P has at least one substituent R^1. In one embodiment of the invention P has one substituent R^1. In a preferred embodiment, the substituent R^1 is at the meta position relative to X^7. In another embodiment of the invention P has 2 substituents R^1. In a preferred embodiment the substituents R^1 are in the 2-position (meta) and 5-position (ortho) to X^7. In one embodiment of the invention R1 is selected from hydrogen, hydroxy, halo, nitro, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{2-6}alkenyl, OC_{2-6}alkenyl, C_{2-6}alkynyl, OC_{2-6}alkynyl, C_{0-6}alkyiC_{3-6}cycloalkyl, OC_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, CHO, $(CO)R^5$, $O(CO)R^5$, $O(CO)OR^5$, $O(CN)OR^5$, C_{1-6}alkylOR^5, OC_{2-6}alkylOR^5, C_{1-6}alkyl$(CO)R^5$, OC_{1-6}alkyl$(CO)R^5$, C_{0-6}alkylCO_2R^5, OC_{1-6}alkylCO_2R^5, C_{0-6}alkylcyano, OC_{2-6}alkylcyano, C_{0-6}alkylNR^5R^6, OC_{2-6}alkylNR^5R^6, C_{1-6}alkyl$(CO)NR^5R^6$, OC_{1-6}alkyl$(CO)NR^5R^6$, C_{0-6}alkyl$NR^5(CO)R^6$, OC_{2-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)NR^5R^6$, C_{0-6}alkylSR^5, OC_{2-6}alkylSR^5, C_{0-6}alkyl$(SO)R^5$, OC_{2-6}alkyl$(SO)R^5$, C_{0-6}alkylSO_2R^5, OC_{2-6}alkylSO_2R^5, C_{0-6}alkyl$(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)NR^5R^6$,C_{0-6}alkyl$NR^5(SO_2)R^6$, OC_{2-6}alkyl$NR^5(SO_2)R^6$, C_{0-6}alkyl$NR^5(SO_2)NR^5R^6$, OC_{2-6}alkyl$NR^5(SO_2)NR^5R^6$, $(CO)NR^5R^6$, $O(CO)NR^5R^6$, NR^5OR^6, C_{0-6}alkyl$NR^5(CO)OR^6$, OC_{2-6}alkyl$NR^5(CO)OR^6$, SO_3R^5 and a 5- or 6-membered ring containing one or more atoms independently selected from the group consisting of C, N, O and S. In another embodiment of the invention R^1 is selected from halo, C_{1-6}alkyl, $-OC_{1-6}$alkyl, C_{0-6}alkylcyano. In another embodiment R^1 is selected from Cl, F, CN and methyl.

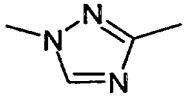
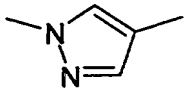
Embodiments of the invention include those wherein R^5 and R^6 are selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl and aryl.

Formula I allows for variables X^7 and X^8. In one embodiment of the invention X^7 and X^8 are selected from C and N, such that when X^7 is N, X^8 is C and when X^7 is C, X^8 is N.

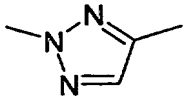
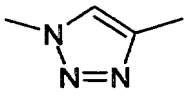
Formulas I and II provide variables X^1, X^2 and X^3. In one embodiment of the invention X^1, X^2 and X^3 are independently selected from CR^4, N, O and S such that at least one of X^1, X^2, and X^3 is not N. In another embodiment of the invention at least one of X^1, X^2 and X^3 is not CR^4. In another embodiment of the invention X^1 and X^2 are independently selected from the group consisting of CR^4, and N, and X^3 is selected from the group consisting of CR^4, N, and O such that at least one of X^1 X^2 and X^3 is not N.

In still another embodiment of the invention X^1 X^2 and X^3 are selected such that the ring that they form is one of:

a)  , b)  , c)  , d)  ,

e)  , and f)  .

In still a further embodiment of the invention X^1 X^2 and X^3 are selected such that the ring that they form is one of:

c)  , d)  .

When X^1, X^2 or X^3 is CR^4, the variable R^4 is selected from H, =O, C_{1-6}alkyl, OH. In particular embodiments R^4 is H, =O. In a preferred embodiment R^4 is H.

A linker group comprised of a carbon atom and a variable X^4, joins the five membered ring containing variables X^1 X^2 and X^3 to the ring Q. The carbon atom has one or two substituents R^3 which are independently selected from H, C_{1-6}alkyl, hydroxy, C_{0-6}alkylcyano, oxo, $=NR^5$, $=NOR^5$, C_{1-4}alkylhalo, halo, C3-7cycloalkyl, $O(CO)C_{1-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-4}alkyl$(SO_2)C_{0-4}$alkyl, $(SO)C_{0-4}$alkyl, $(SO_2)C_{0-4}$alkyl, OC_{1-4}alkyl, C_{1-4}alkylOR^5 and C_{0-4}alkylNR^5R^6. In a preferred embodiment R^3 is selected from the group consisting of H and C_{1-6}alkyl. Preferably R^3 is H or methyl.

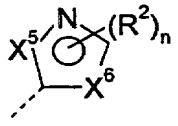
The variable X^4 is selected from CR^7R^8, NR^7, O, S, SO, and SO_2. In a particular embodiment X^4 is selected from CR^7R^8, NR^7, O, S. The variables R^7 and R^8 are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl and aryl. In one embodiment R^7 and R^8 are independently selected from hydrogen and C_{1-6}alkyl. In particular embodiments R^7 and R^8 are independently selected from hydrogen and methyl.

In embodiments of the invention, R^3 can optionally bond to the ring Q, thereby forming a fused cyclic group.

In other embodiments of the invention R^7 or R^8 can optionally bond to R^3 to form a cyclic group.

In still other embodiments of the invention R^7 or R^8 can optionally bond to Q to form a fused cyclic group.

Formula 1 provides a ring Q, which contains 5- to 7-members and may be cycloalkyl, heterocycloalkyl, aryl or heteroaryl. In particular embodiments of the invention the ring Q is a 5-memebred ring. In more particular embodiments of the invention Q is a heteroaromatic ring. In still more particular embodiments of the invention Q is:



as shown in formula II.

As provided in formula II the ring contains two variables X^5 and X^6. In embodiments of the invention X^5 and X^6 are independently selected from C, N, O and S. In one preferred embodiment of the invention X^5 and X^6 are both N. In another embodiment X^5 is C and X^6 is N. In still another preferred embodiment X^5 is N and X^6 is O.

Formulas I and II allow for 0 to 4 variables R^2 on the ring Q or the ring containing X^5 and X^6, respectively. In one embodiment of the invention there is provided one variable R^2. In another embodiment of the invention there is provided two variables R^2. The variables, R^2 are independently selected from hydrogen, hydroxy, C_{0-6}alkylcyano, $=NR^5$, $=NOR^5$, C_{1-4}alkylhalo, halo, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylcycloalkyl, C_{0-6}alkylheterocycloalkyl, OC_{1-4}alkyl, OC_{0-6}alkylaryl, $O(CO)C_{1-4}$alkyl, $(CO)OC_{1-4}$alkyl, C_{0-4}alkyl$(S)C_{0-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-4}alkyl$(SO_2)C_{0-4}$alkyl, $(SO)C_{0-4}$alkyl, $(SO_2)C_{0-4}$alkyl, C_{1-4}alkylOR^5, C_{0-4}alkylNR^5R^6 and a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O and S, which ring may optionally be fused with a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N and O and wherein said ring and said fused ring may be substituted by one or more A; In a preferred embodiment of the invention the variable R^2 is selected from H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{3-6}cycloalkyl and C_{0-6}alkylheteroary. In a preferred embodiment of the invention there is a variable R^2 that is selected from C_{0-6}alkylaryl, and C_{0-6}alkylheteroary, more preferably from aryl and

heteroaryl and still more preferably from 4-pyridyl, 3-pyridyl and phenyl. In another preferred embodiment when there are two variables R^2 the first is selected from the group aryl and heteroaryl, and the second is selected from C_{1-6}alkyl and C_{3-6}cycloalkyl. In another preferred embodiment of the invention one variable is 4-pyridyl and the other is methyl. In another preferred embodiment of the invention one variable is 4-pyridyl and the other is cyclopropyl.

Formulas I and II further allow the variable R^2 and any C_{1-6}alkyl, aryl, or heteroaryl group defined under R^1 and R^3 to be further substituted with one or more variables A.
The variables A are independently selected from hydrogen, hydroxy, halo, nitro, oxo, C_{0-6}alkylcyano, C_{0-4}alkylC_{3-6}cycloalkyl, C_{1-6}alkyl, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{2-6}alkenyl, C_{0-3}alkylaryl, C_{0-6}alkylOR^5, OC_{2-6}alkylOR^5, C_{1-6}alkylSR^5, OC_{2-6}alkylSR^5, $(CO)R^5$, $O(CO)R^5$, OC_{2-6}alkylcyano, OC_{1-6}alkylCO_2R^5, $O(CO)OR^5$, OC_{1-6}alkyl$(CO)R^5$, C_{1-6}alkyl$(CO)R^5$, NR^5OR^6, C_{1-6}alkylNR5R6, OC_{2-6}alkylNR^5R^6, C_{0-6}alkyl$(CO)NR^5R^6$, OC_{1-6}alkyl$(CO)NR^5R^6$, OC_{2-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)R^6$, C_{0-6}alkyl$NR^5(CO)NR^5R^6$, $O(CO)NR^5R^6$, C_{0-6}alkyl$(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)NR^5R^6$, C_{0-6}alkyl$NR^5(SO_2)R^6$, OC_{2-6}alkyl$NR^5(SO_2)R^6$, SO_3R^5, C_{1-6}alkyl$NR^5(SO_2)NR^5R^6$, OC_{2-6}alkyl$(SO_2)R^5$, C_{0-6}alkyl$(SO_2)R^5$, C_{0-6}alkyl$(SO)R^5$, OC_{2-6}alkyl$(SO)R^5$ and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S. In further embodiment of the invention A is selected from Cl, F, CN, Me, OMe, and OH.

Embodiments of the invention include salt forms of the compounds of Formula I and II. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of Formula I.

A suitable pharmaceutically acceptable salt of the compounds of the invention is, for example, an acid-addition salt, for example an inorganic or organic acid. In addition, a suitable pharmaceutically acceptable salt of the compounds of the invention is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base.
Other pharmaceutically acceptable salts and methods of preparing these salts may be found in, for example, Remington's Pharmaceutical Sciences (18^{th} Edition, Mack Publishing Co.) 1990.

Some compounds of formula I may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomeric and geometric isomers.

The invention also relates to any and all tautomeric forms of the compounds of Formula I and II.

The invention further relates to hydrate and solvate forms of the compounds of Formula I and II

Pharmaceutical composition

According to one aspect of the present invention there is provided a pharmaceutical composition comprising as active ingredient a therapeutically effective amount of the compound of Formula I or more particularly a compound of Formula II, or salts, solvates or solvated salts thereof, in association with one or more pharmaceutically acceptable diluent, excipients and/or inert carrier.

The composition may be in a form suitable for oral administration, for example as a tablet, pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration e.g. as an ointment, patch or cream or for rectal administration e.g. as a suppository.

In general the above compositions may be prepared in a conventional manner using one or more conventional excipients, pharmaceutical acceptable diluents and/or inert carriers.

Suitable daily doses of the compounds of formula I in the treatment of a mammal, including man are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration.

The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, severity of the illness being treated, the route of administration, the age, weight and sex of the patient and the particular compound

being used, and may be determined by a physician.

Medical use

It has been found that the compounds according to the present invention, exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor (mGluR) subtypes. Accordingly, the compounds of the present invention are expected to be useful in the treatment of conditions associated with excitatory activation of mGluR5 and for inhibiting neuronal damage caused by excitatory activation of mGluR5. The compounds may be used to produce an inhibitory effect of mGluR5 in mammals, including man.

The mGluR Group I receptor including mGluR5 are highly expressed in the central and peripheral nervous system and in other tissues. Thus, it is expected that the compounds of the invention are well suited for the treatment of mGluR5-mediated disorders such as acute and chronic neurological and psychiatric disorders, gastrointestinal disorders, and chronic and acute pain disorders.

The invention relates to compounds of Formula I and Formula II, as defined hereinbefore, for use in therapy.

The invention relates to compounds of Formula I and Formula II, as defined hereinbefore, for use in treatment of mGluR5-mediated disorders.

The invention relates to compounds of Formula I and Formula II, as defined hereinbefore, for use in treatment of Alzheimer's disease senile dementia, AIDS-induced dementia, Parkinson's disease, amylotropic lateral sclerosis, Huntington's Chorea, migraine, epilepsy, schizophrenia, depression, anxiety, acute anxiety, ophthalmological disorders such as retinopathies, diabetic retinopathies, glaucoma, auditory neuropathic disorders such as tinnitus, chemotherapy induced neuropathies, post-herpetic neuralgia and trigeminal neuralgia, tolerance, dependency, Fragile X, autism, mental retardation, schizophrenia and Down's Syndrome.

The invention relates to compounds of Formula I and Formula II, as defined hereinbefore, for use in treatment of pain related to migraine, inflammatory pain, neuropathic pain

disorders such as diabetic neuropathies, arthritis and rheumatoid diseases, low back pain, post-operative pain and pain associated with various conditions including angina, renal or biliary colic, menstruation, migraine and gout.

The invention relates to compounds of Formula I and Formula II as defined hereinbefore, for use in treatment of stroke, head trauma, anoxic and ischemic injuries, hypoglycemia, cardiovascular diseases and epilepsy.

The present invention relates also to the use of a compound of Formula I and Formula II as defined hereinbefore, in the manufacture of a medicament for the treatment of mGluR Group I receptor-mediated disorders and any disorder listed above.

One embodiment of the invention relates to the use of a compound according to Formula I and Formula II in the treatment of gastrointestinal disorders.

Another embodiment of the invention relates to the use of a compound according to Formula I and Formula II, for the manufacture of a medicament for the inhibition of transient lower esophageal sphincter relaxations, for the treatment of GERD, for the prevention of G.I. reflux, for the treatment regurgitation, treatment of asthma, treatment of laryngitis, treatment of lung disease and for the management of failure to thrive.

A further embodiment of the invention is the use of a compound according to formula I for the manufacture of a medicament for the treatment or prevention of functional gastrointestinal disorders, such as functional dyspepsia (FD). Yet another aspect of the invention is the use of a compound according to formula I for the manufacture of a medicament for the treatment or prevention of irritable bowel syndrome (IBS), such as constipation predominant IBS, diarrhea predominant IBS or alternating bowel movement predominant IBS.

A further aspect of the invention is the use of a compound according to formula I for the manufacture of a medicament for the treatment or prevention of obesity and obesity related conditions, as well as treating eating disorders by inhibition of excessive food intake and the resulting obesity and complications associated therewith.

These and other aspects of the present invention are described in greater detail herein below.

The invention also provides a method of treatment of mGluR5-mediated disorders and any disorder listed above, in a patient suffering from, or at risk of, said condition, which comprises administering to the patient an effective amount of a compound of Formula I and Formula II, as hereinbefore defined.

The dose required for the therapeutic or preventive treatment of a particular disorder will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated.

In the context of the present specification, the term "therapy" and "treatment" includes prevention or prophylaxis, unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

In this specification, unless stated otherwise, the term "antagonist" and "inhibitor" shall mean a compound that by any means, partly or completely, blocks the transduction pathway leading to the production of a response by the ligand.

The term "disorder", unless stated otherwise, means any condition and disease associated with metabotropic glutamate receptor activity.

Non- Medical use

In addition to their use in therapeutic medicine, the compounds of Formula I and Formula II, salts or hydrates thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of mGluR related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

Methods of Preparation

Another aspect of the present invention provides processes for preparing compounds of Formula I and II, or salts or hydrates thereof. Processes for the preparation of the compounds in the present invention are described herein.

Throughout the following description of such processes it is to be understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one

skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis", T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, (1999). It is also to be understood that a transformation of a group or substituent into another group or substituent by chemical manipulation can be conducted on any intermediate or final product on the synthetic path toward the final product, in which the possible type of transformation is limited only by inherent incompatibility of other functionalities carried by the molecule at that stage to the conditions or reagents employed in the transformation. Such inherent incompatibilities, and ways to circumvent them by carrying out appropriate transformations and synthetic steps in a suitable order, will be readily understood to the one skilled in the art of organic synthesis. Examples of transformations are given below, and it is to be understood that the described transformations are not limited only to the generic groups or substituents for which the transformations are exemplified. References and descriptions on other suitable transformations are given in "Comprehensive Organic Transformations – A Guide to Functional Group Preparations" R. C. Larock, VHC Publishers, Inc. (1989). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March, 4th ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994). Techniques for purification of intermediates and final products include for example, straight and reversed phase chromatography on column or rotating plate, recrystallisation, distillation and liquid-liquid or solid-liquid extraction, which will be readily understood by the one skilled in the art. The definitions of substituents and groups are as in formula I except where defined differently. The term "room temperature" and "ambient temperature" shall mean, unless otherwise specified, a temperature between 16 and 25 °C.

The term "reflux" shall mean, unless otherwise stated, in reference to an employed solvent a temperature at or above the boiling point of named solvent.

Abbreviations

atm	atmosphere
aq.	aqueous
CDI	N,N'-Carbonyldiimidazole

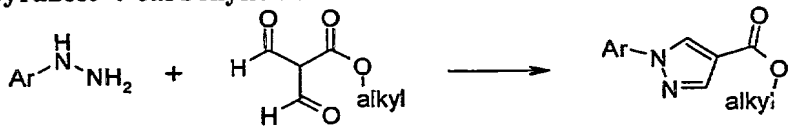
DCC	N,N-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEA	N,N-Diisopropyl ethylamine
DIC	N,N'-Diisopropylcarbodiimide
DMAP	N,N-Dimethyl-4-aminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
EA	Ethyl acetate
EDCl	N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride
EtOAc	Ethyl acetate
Et_2O	Diethylether
h	hour(s)
HOBt	N-Hydroxybenzotriazole
HBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
MCPBA	*m*-chlorbenzoic acid
MeCN	acetonitrile
MeOH	Methanol
min	minutes
nBuLi	1-butyl lithium
Novozyme 435®	Polymer supported *Candida Antartica Lipase* (Novozymes, Bagsvaerd, Denmark)
o.n.	over night
RT, rt, r.t.	room temperature
TEA	Triethylamine
THF	Tetrahydrofuran
BOC	*tert*-butoxycarbonyl
*n*Bu	normal butyl
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
PPTS	pyridinium *p*-toluenesulfonate
TBAF	tetrabutylammonium fluoride
pTsOH	*p*-toluenesulfonic acid
SPE	solid phase extraction (usually containing silica gel for mini-chromatography)
sat.	saturated
n-BuLi	1-butyllithium

OMs	mesylate or methane sulfonate ester
OTs	tosylate, toluene sulfonate or 4-methylbenzene sulfonate ester
HetAr	heteroaryl
NaOAc	sodium acetate
EtOAc	ethyl acetate
EtOH	ethanol
EtI	iodoethane
Et	ethyl
MeI	iodomethane
MeMgCl	methyl magnesium chloride
Me	methyl
NMR	nuclear magnetic resonance
HPLC	high performance liquid chromatography
LCMS	HPLC mass spec

Preparation of intermediates

The intermediates provided in synthetic paths given below, are useful for further preparation of compounds of formula I or II. Other starting materials are either commercially available or can be prepared via methods described in the literature. The synthetic pathways described below are non-limiting examples of preparations that can be used. One of skill in the art would understand other pathways might be used.

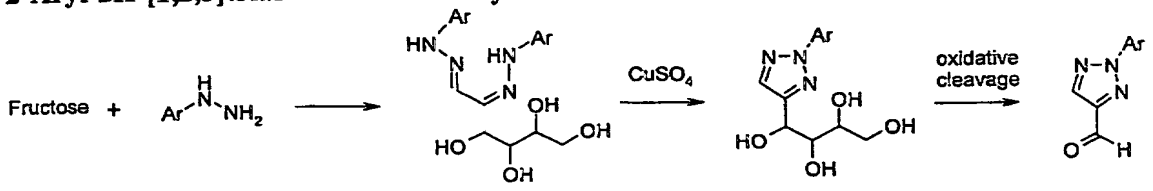
1-Aryl-1H-pyrazole-4-carboxylic acid esters



Scheme 1

With reference to scheme 1, pyrazoles carboxylic acid esters may be obtained by reaction of 3-arylhydrazines with alkyl 2-formyl-3-oxopropanoate in solvents such ethanol at temperatures from 40 to 140 °C. [Holzer, W.; Seiringer, G.; J.Heterocycl.Chem.; 1993, 30; 865-872.]

2-Aryl-2H-[1,2,3]triazole-4-carbaldehydes

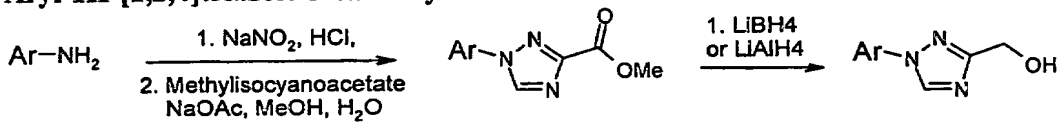


Scheme 2

With reference to scheme 2, [1,2,3]triazole-4-carbaldehydes may be obtained from aryl glucosetriazoles by oxidative cleavage, employing for example periodic acid in aqueous mixtures of dioxane or THF at–20 to 120 °C. Aryl glucosetriazoles may be obtained by cyclization of the intermediate aryl glucosazone in the presence of copper (II) sulfate in aqueous mixtures of for example dioxane or THF at–20 to 120 °C. The aryl glucosazone in turn is made by coupling of arylhydrazines with fructose in acetic acid and water at –20 to 120 °C.

[Buckler,R.;Hartzler, H.; Kurchacova, E.; Nichols, G.; Phillips, B.; J. Med. Chem.; 1978; 21(12); 1254-1260, and Riebsomer, J.; Sumrell, G.; J. Org. Chem.; 1948; 13(6); 807-814]

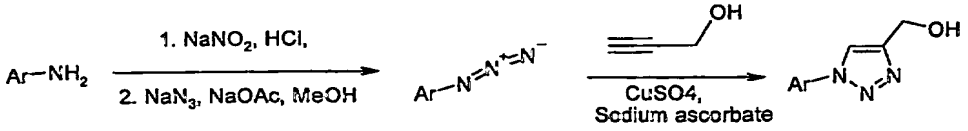
1-Aryl-1H-[1,2,4]triazole-3-carboxylic acid esters



Scheme 3

With reference to scheme 3, 1-aryl-1*H*-1,2,4-triazole-derivatives may be prepared from commercially available anilines by initial diazotization followed by cyclization to the 1,2,4-triazole using methylisocyanocynates (See Matsumoto, K., Suzuki, M., Tomie, M., Yoneda, N. and Miyoshi, M.: *Synthesis*, **1975**, 609 – 610). The resulting ester is then subjected to reduction to afford the corresponding alcohol (See Genin, M.J. et al: *J. Med. Chem.* **2000**, 43, 953-970).

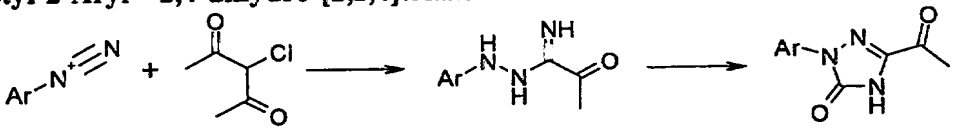
(1-Aryl-1H-[1,2,3]triazol-4-yl)-alkyl alcohols



Scheme 4

With reference to Scheme 4, 1-aryl-1*H*-1,2,3-triazole-derivatives may be prepared from commercially available anilines by initial diazotization followed by conversion of the diazonium salt to the corresponding azide using NaN_3. The aryl azide may then be cyclized onto propargyl alcohol in a regiospecific manner using catalytic $CuSO_4$ to afford the [1,2,3]triazole alcohol intermediate (See Rostovtsev, V.V., Green, L.G., Fokin, V.V., Sharpless, K.B.: *Angew., Chem. Intl. Ed.* 2002, 41, 14, 2596 – 2599.)

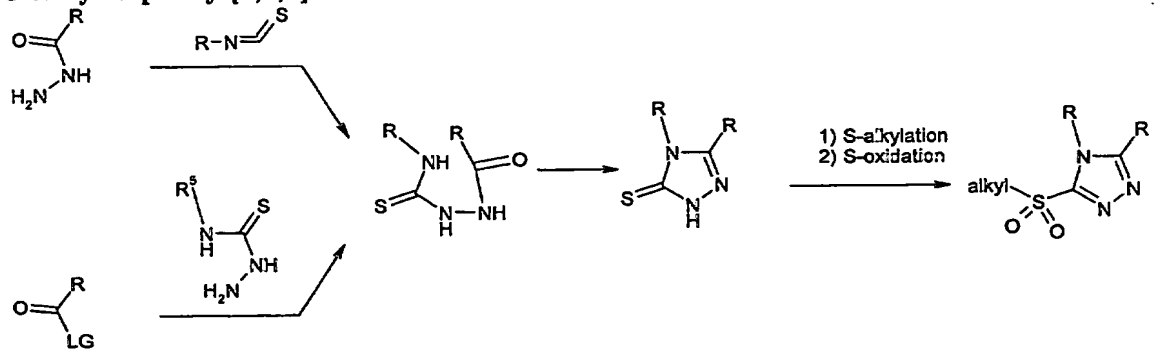
5-Acetyl-2-Aryl—2,4-dihydro-[1,2,4]triazol-3-ones



Scheme 5

With reference to scheme 5, 5-acetyl-[1,2,4]triazole-3-ones may be made by cyclization of 2-oxo-N'-arylpropanimidohydrazide with carbonyl dichloride or carbonyl diimidazole in solvents such as toluene, dioxane, or THF at temperatures from 40 to 140 °C. 2-Oxo-N'-arylpropanimidohydrazides may be synthesized by reaction of aryldiazonium salts, for example the tetrafluoroborate salt, with 3-haloopentane-2,4-diones, for example with halo=chloro, in the presence of potassium acetate in methanol/water at temperatures from – 40 to 40 °C to give an intermediate which is subsequently treated *in-situ* with ammonia in for example methanol, ethanol, dioxane or THF [US patent #4,400,517, 1983].

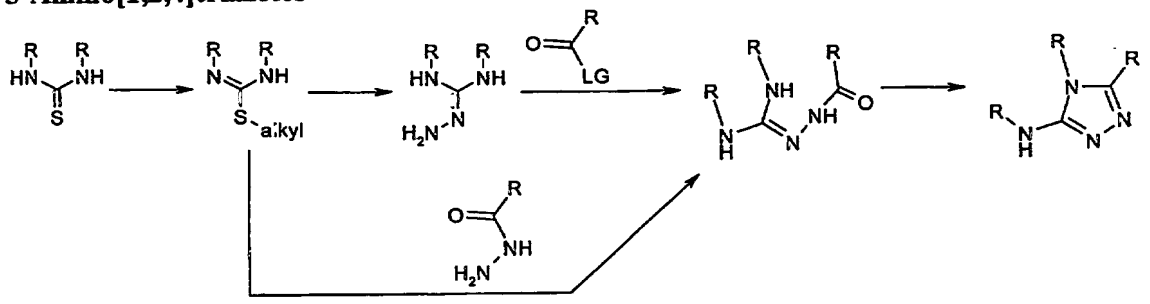
3-Alkylsulphonyl[1,2,4]triazoles



Scheme 6

With reference to scheme 6, 3-alkylsulphonyl[1,2,4]triazoles may be prepared from the corresponding dihydro-[1,2,4]triazolethiones by initial alkylation of the sulphur atom with primary alkyl halides such as MeI and EtI (alkyl is Me and Et respectively) in MeOH, EtOH, THF, acetone or the like at –30 to 100 °C, followed by oxidation of the sulphur atom using for example $KMnO_4$ in mixtures of water and acetic acid, or MCPBA in DCM, at –20 to 120 °C, or by using any other suitable oxidant. Dihydro[1,2,4]triazolethiones are for example prepared by initial N-acylation of a thiosemicarbazide, using any suitable acylating agent such as acid chlorides, bromides or fluorides (LG is Cl, Br or F) in for example pyridine, or acids (LG is OH), that are activated *in situ* by the treatment with standard activating reagents such as DCC, DIC, EDCl or HBTU, with or without the presence of co-reagents such as HOBt or DMAP, in suitable solvents such as DMF, DCM, THF, or MeCN at a temperature from –20 to 100 °C, followed by ring closure of the initially formed acyclic intermediate either spontaneously under the conditions of the acylation, or by heating at 50 to 150 °C in pyridine or in aqueous solvents in the presence of a base, such as $NaHCO_3$ or Na_2CO_3, with or without co-solvents such as dioxane, THF, MeOH, EtOH or DMF. This acyclic intermediate can also be formed by treatment of the proper acyl hydrazide with a suitable isothiocyanate in for example 2-propanol, DCM, THF or the like at –20 to 120 °C.

3-Amino[1,2,4]triazoles



Scheme 7

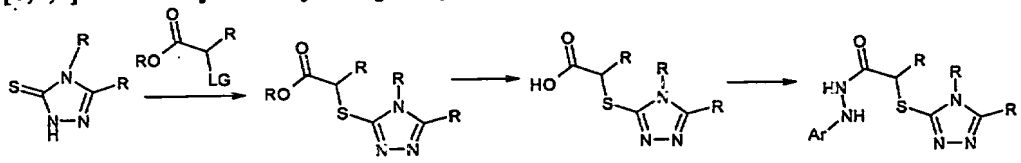
With reference to scheme 7, 3-amino[1,2,4]triazoles may be obtained by treating carbonohydrazonic diamides with a suitable acylating agent carrying a leaving group LG in

suitable solvent such as THF, pyridine or DMF at -20 to 100 °C. The reaction initially leads to an intermediate that either forms a triazole ring spontaneously, or can be made to do so by heating at 50 to 200 °C in for example pyridine or DMF. The leaving group LG may be chloro or any other suitable leaving group as for example generated by *in situ* treatment of the corresponding acid (LG is OH) with standard activating reagents as described herein above. Carbonohydrazonic diamides may be generated from isothioureas, in which the S-alkyl (for example S-Me or S-Et) moiety acts as a leaving group upon treatment with hydrazine in solvents such as pyridine, methanol, ethanol, 2-propanol, THF or the like at –20 to 180 °C. The intermediate may also be directly generated by treatment of isothioureas with acyl hydrazides under the same conditions as described for the reaction with hydrazine. Isothioureas are obtained by S-alkylation of the corresponding thioureas with for example MeI or EtI in acetone, EtOH, THF, DCM or the like at –100 to 100 °C.

Other 5-membered heteroaromatics

Other methods for the preparation of 5-membered heteroaromatic rings that are useful for the preparation of compounds of formula I are found in the literature and in books such as "Katritzky and A.F. Pozharskii, *Handbook of Heterocyclic Chemistry*, Pergamon Press, 2nd Ed. 2000."

[1,2,4]triazol-3-ylsulfanyl N'-phenyl acylhydrazide

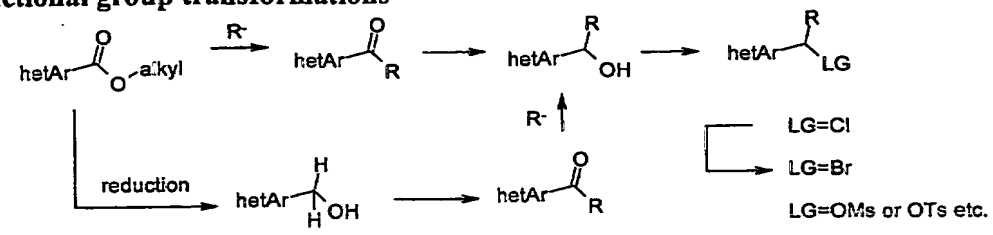


Scheme 8

With reference to scheme 8, [1,2,4]triazol-3-ylsulfanyl N'-aryl acylhydrazides may be obtained by reaction of the corresponding acid with aryl hydrazines by standard coupling conditions as described herein above. The acid may be obtained by hydrolysis of its corresponding alkyl ester using standard conditions such as potassium hydroxide in solvents such as methanol or THF/water at temperatures from 0 to 100 °C. Alkylation of a

triazole thione with for example methyl chloro acetate or propionate under standard conditions as described herein below gives the alkyl ester.

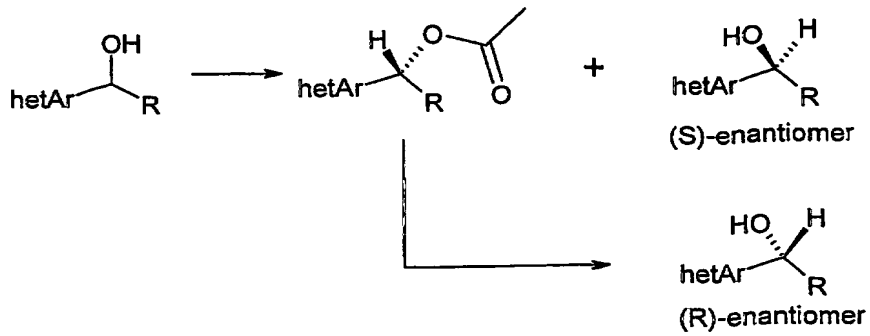
Functional group transformations



Scheme 9

With reference to scheme 9, aliphatic alcohols may for example be converted by standard methods to the corresponding halides by the use of for example triphenylphosphine in combination with either iodine, N-bromosuccinimide or N-chlorosuccinimide, or alternatively by treatment with tribromophosphine or thionyl chloride. Alcohols may be transformed to other leaving groups such as mesylates or tosylates by employing the appropriate sulfonyl halide or sulfonyl anhydride in the presence of a non-nucleophilic base together with the alcohol to obtain the corresponding sulfonates. Chlorides or sulfonates may be converted to the corresponding bromides or iodides by treatment with bromide salts, for example LiBr, or iodide salts, such as LiI. Further standard methods to obtain alcohols include the reduction of the corresponding carbonyl containing groups such as methyl or ethyl esters, aldehydes or ketones, by employing common reducing agents such as boranes, lithium borohydride, lithium aluminium hydride, or hydrogen in the presence of a transition metal catalyst such as complexes of for example ruthenium or iridium, or alternatively palladium on charcoal. Ketones and secondary alcohols may be obtained by treatment of carboxylic acid esters and aldehydes respectively, with the appropriate carbon nucleophile, such as alkyl-Grignard reagents or alkyl-lithium reagents according to standard protocols. Heteroaromatic aldehydes may be prepared from the corresponding primary alcohols by oxidation procedures well known to the one skilled in the art, such as the employment of MnO_2 as oxidant, or by Swern oxidation.

Stereoselective preparation of chiral secondary alcohols



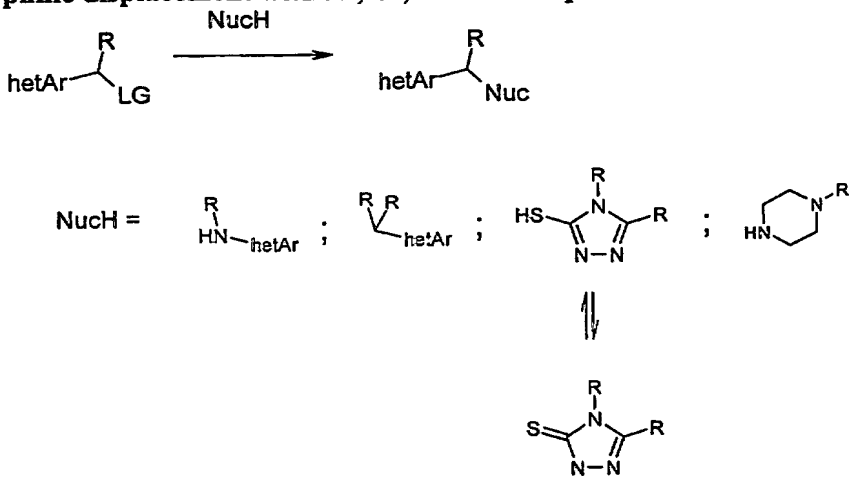
Scheme 9a

Enantiomerically pure or enriched products, as depicted in scheme 9a, (R is Me or Et) are obtained by kinetic resolution of racemic or scalemic secondary alcohols using enzyme-catalyzed acetylation with for example polymer bound *Candida Antarctica Lipase* (Novozyme 435®), or other esterases, for example *Candida rugosa* or *Pseudomonas fluorescens*, in organic solvents such as toluene, tert-butyl methyl ether, tert-butanol or DCM at temperatures from 0 to 90 °C, using acetylating reagents such as vinyl acetate, other substituted alkyl acetates, pentafluorophenyl acetate or nitro- or halophenyl acetates, which yields the enriched (*R*)-acetate and the enriched (*S*)-alcohol. The (*R*)-acetate may be hydrolyzed to the corresponding alcohol by e.g. lithium hydroxide in mixtures of THF and water or by any other methods as described herein below, to yield the opposite enantiomerically enriched or pure alcohol.

Preparation of final compounds

The subsequent described non-limiting methods of preparation of final compounds of formula I are illustrated and exemplified by drawings in which the generic groups, or other structural elements of the intermediates correspond to those of formula I. It is to be understood that an intermediate containing any other generic group or structural element than those of formula I can be used in the exemplified reactions, provided that this group or element does not hinder the reaction and that it can be chemically converted to the corresponding group or element of formula I at a later stage which is known to the one skilled in the art.

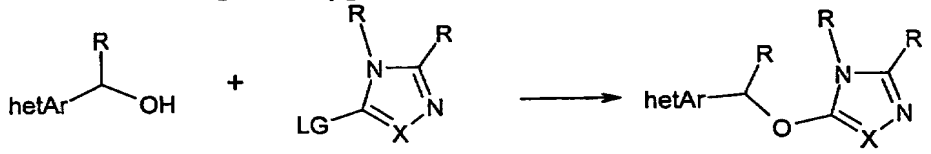
By nucleophilic displacement with N-, C-, or S-nucleophiles



Scheme 10

With reference to scheme 10, compounds of formula I may for example be prepared by bond formation through nucleophilic displacement of a leaving group (LG) in which the nucleophilic atom might be the amino-nitrogen atom of a heterocyclic amine, the alpha-carbon of an alkyl substituted heteroaromatic, the sulphur atom of a [1,2,4]triazole-3-thiol tautomer and the nitrogen atom of a secondary aliphatic amine, such as piperazine derivatives. Amino-nitrogen atoms of heterocyclic amines, and the *alpha*-carbons of alkyl substituted heteroaromatics, are generally not reactive in the neutral protonated form and are therefore preferably fully or partly converted to more nucleophilic anionic forms by treatment with bases in suitable solvents such as lithium diispropylamine or n-BuLi in THF, diethyl ether or toluene, or NaH in for example DMF, or K_2CO_3 or Cs_2CO_3 in acetonitrile or ketones such as 2-butanone, either *in situ* or just before the reaction with a suitable electrophile carrying a leaving group, at a temperature from –100 to 150 °C. The sulphur atoms of [1,2,4]triazole-3-thiols and the nitrogen atoms of secondary aliphatic amines may be nucleophilic enough to displace a leaving group in the corresponding neutral forms, but preferably a base such as K_2CO_3, Cs_2CO_3, TEA, DEA or the like is added to facilitate the reaction in solvents such as acetonitrile, DMF or DCM at 0 to 150 °C. For carbon nucleophiles, the leaving group is preferable bromo, for other nucleophiles examples of suitable leaving groups LG include chloro, bromo, OMs and OTs. Optionally, catalytic or stoichiometric amounts of an alkali metal iodide, such as LiI, may be present in the reaction to facilitate the same through *in situ* displacement of the leaving group to iodo.

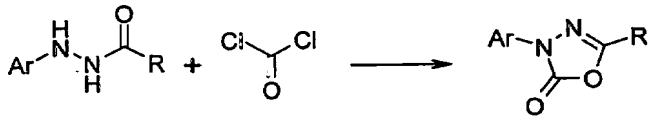
By connection to nucleophilic oxygen



Scheme 11

With reference to scheme 11, compounds of formula I (wherein X^4 as drawn in formula I is O) may be prepared by bond formation through nucleophilic replacement of a leaving group (LG) in which an alcohol acts as O-nucleophile under basic conditions. The base used may include strong hydridic bases, for example, NaH or milder bases, such as Cs_2CO_3, at temperatures from 0 to 80 °C in polar aprotic solvents such as DMF or acetonitrile, whereas for chiral alcohols the preferred base is Cs_2CO_3 in order to obtain enantiomerically pure products directly. Examples of suitable leaving groups are alkylsulfonyls, such as methanesulfonyl and ethanesulfonyl, and halogens, such as chloro.

By ring-formation to 5-substituted 3-aryl-1,3,4-oxadiazol-2(3H)-one



Scheme 12

With reference to scheme 12, compounds of formula I may be prepared by condensing suitably substituted acyl hydrazides with phosgene in the presence of bases, such as TEA or DEA, in solvents such as dioxane, THF, DCM, toluene or DMF at 50 to 200 °C as described for similar oxadiazolones in e.g. J. Med. Chem. 1993, 36, 1157-1167.

The invention further relates to the following compounds, which may be used as intermediates in the preparation of compounds of formula I;

Methyl-(4-methyl-5-pyridin-4-yl-4H-[1,2,4]triazol-3-yl)-amine

4-Methyl-5-pyridin-3-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione

4-Methyl-5-pyridin-4-yl-2,4-dihydro-[1,2,4]triazole-3-thione

4-Cyclopropyl-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione

4-(4-Methyl-5-methylsulfanyl-4H-[1,2,4]triazol-3-yl)-pyridine

4-(4-Cyclopropyl-5-methylsulfanyl-4H-[1,2,4]triazol-3-yl)-pyridine

4-(5-Methanesulfonyl-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine

4-(4-Cyclopropyl-5-methanesulfonyl-4H-[1,2,4]triazol-3-yl)-pyridine

Methyl [(4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)thio]acetate

[(4-Methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)thio]acetic acid

N'-(3-Chlorophenyl)-2-[(4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)thio]acetohydrazide

5-(1-Chloroethyl)-2-(3-chlorophenyl)-1,2-dihydro-3H-1,2,4-triazol-3-one

2-(3-chlorophenyl)-5-(1-hydroxyethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

5-acetyl-2-(3-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

N'-(3-chlorophenyl)-2-oxopropanimidohydrazide

Ethyl 1-(3-chlorophenyl)-1H-pyrazole-4-carboxylate

[1-(3-chlorophenyl)-1H-pyrazol-4-yl]methanol

1-(3-chlorophenyl)-1H-pyrazole-4-carbaldehyde

1-[1-(3-chlorophenyl)-1H-pyrazol-4-yl]ethanol

1-[2-(3-chlorophenyl)-2H-1,2,3-triazol-4-yl]ethanol

4-(1-chloroethyl)-2-(3-chlorophenyl)-2H-1,2,3-triazole

1-(3-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid methyl ester

[1-(3-Chloro-phenyl)-1H-[1,2,4]triazol-3-yl]-methanol

Methanesulfonic acid 1-(3-chloro-phenyl)-1H-[1,2,4]triazol-3-ylmethyl ester

[1-(3-Chloro-phenyl)-1H-[1,2,3]triazol-4-yl]-methanol

Methanesulfonic acid 1-(3-chloro-phenyl)-1H-[1,2,3]triazol-4-ylmethyl ester

Examples

The invention will now be illustrated by the following non-limiting examples.

General methods

All starting materials are commercially available or earlier described in the literature.

The ^{1}H and ^{13}C NMR spectra were recorded either on Bruker 300, Bruker DPX400 or Varian +400 spectrometers operating at 300, 400 and 400 MHz for ^{1}H NMR respectively, using TMS or the residual solvent signal as reference, in deuterated chloroform as solvent unless otherwise indicated. All reported chemical shifts are in ppm on the delta-scale, and the fine splitting of the signals as appearing in the recordings (s: singlet, br s: broad singlet, d: doublet, t: triplet, q: quartet, m: multiplet).

Analytical in line liquid chromatography separations followed by mass spectra detections, were recorded on a Waters LCMS consisting of an Alliance 2795 (LC) and a ZQ single quadropole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source operated in a positive and/or negative ion mode. The ion spray voltage was ±3 kV and the mass spectrometer was scanned from m/z 100-700 at a scan time of 0.8 s. To the column, X-Terra MS, Waters, C8, 2.1 x 50mm, 3.5 mm, was applied a linear gradient from 5 % to 100% acetonitrile in10 mM ammonium acetate (aq.), or in 0.1% TFA (aq.).

Preparative reversed phase chromatography was run on a Gilson autopreparative HPLC with a diode array detector using an XTerra MS C8, 19x300mm, 7mm as column.

Purification by a chromatotron was performed on rotating silica gel / gypsum (Merck, 60 PF-254 with calcium sulphate) coated glass sheets, with coating layer of 1, 2, or 4 mm using a TC Research 7924T chromatotron. Purification of products were also done by flash chromatography in silica-filled glass columns.

Microwave heating was performed in a Smith Synthesizer Single-mode microwave cavity producing continuous irradiation at 2450 MHz (Personal Chemistry AB, Uppsala, Sweden).

Example 1

Methyl-(4-methyl-5-pyridin-4-yl-4H-[1,2,4]triazol-3-yl)-amine

A mixture of 1000 mg (4.35 mmol) N-amino-N',N''-dimethyl-guanidine hydriodide (Henry; Smith; J.Amer.Chem.Soc.; 73; 1951; 1858) and 774 mg (4.35 mmol) isonicotinoyl chloride hydrochloride in 3ml of pyridine was heated under microwave irradiation for 5 min at 160°C. Aq. sat. K_2CO_3 was added and the mixture was extracted with $CHCl_3$. The combined organic layer was dried and concentrated. Recrystallization from ethanol, water

and EA gave 216 mg (26%) of the title compound. ^{1}H NMR (d6-DMSO): 2.85 (d, 3 H) 3.45 (s, 3 H) 6.25 (d, 1 H) 7.65 (m, 2 H) 8.67 (m, 2 H)

Example 2

4-Methyl-5-pyridin-3-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione

A solution of 4-methyl-3-thiosemicarbazide (902 mg, 8.58 mmol), nicotinic acid (960 mg, 7.80), EDCl (1.64 g, 8.58 mmol), HOBt (1.16 g, 8.58 mmol) in DMF (10 mL) was stirred at r.t. o.n. The reaction mixture was diluted with EA (100 mL), successively washed with 10% aq. hydrochloric acid, water, sat. aq. Na_2CO_3, water and then brine. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was stirred in NaOH (53.4 mL, 66.7 mmol, 5% aq.) at 60°C o.n. The mixture was cooled to r.t., then brought to pH about 6 using 1N aq. HCl. The aq. phase was sat. with solid NaCl, then extracted with EA. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, concentrated and dried *in vacuo* to give the title compound (180 mg). ^{1}H-NMR: 11.6 (br s, 1H), 8.94 (s, 1H), 8.83 (dd, 1H), 7.98 (m, 1H), 7.51 (dd, 1H), 3.69 (s, 3H).

Example 3

4-Methyl-5-pyridin-4-yl-2,4-dihydro-[1,2,4]triazole-3-thione

Isonicotinoyl chloride hydrochloride (27.5 g, 154.5 mmol) and 4-methyl-3-thiosemicarbazide (16.4 g, 155.9 mmol) were mixed in pyridine (200 ml) and stirred under argon at ambient temperature overnight. After evaporation to dryness, aqueous sodium hydroxide (250 mL, 2M, 500 mmol) was added and the resulting solution was heated at 60°C for 16 h. After cooling to room temperature, the solution was neutralized with 6N hydrochloric acid. The precipitate that formed was collected by filtration to give the title compound (pale yellow solid, 16.4 g, 55%). ^{1}H NMR (DMSO-d6), δ (ppm): 8.78 (dd, 2H), 7.75 (dd, 2H), 3.59 (s, 3H).

Example 4

4-Cyclopropyl-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione

Isonicotinohydrazide (5.4 g, 39 mmol) and cyclopropyl isothiocyanate (4.1 g, 41 mmol) were mixed in 2-propanol (100 ml) and heated to 70 °C o.n. The reaction was cooled to r.t.

and evaporated to dryness. H_2O (170 mL) followed by $NaHCO_3$ (6.7 g, 80 mmol) was added to the residue and the mixture was refluxed o.n. The reaction mixture was cooled to rt, acidified with concentrated hydrochloric acid and the title compound 9.0 g (94%) was collected by filtration. ^1H NMR: 0.63 (m, 2 H) 1.00 (m, 2 H) 3.25 (m, 1 H) 7.75 (d, 2 H) 8.74 (m, 2 H)

Example 5

4-(4-Methyl-5-methylsulfanyl-4H-[1,2,4]triazol-3-yl)-pyridine

To a solution of 4-Methyl-5-pyridin-4-yl-2,4-dihydro-[1,2,4]triazole-3-thione (1000 mg, 5.20 mmol) in 1M sodium hydroxide (10 mL), added a solution of iodomethane (0.52 mL, 8.32 mmol) in ethanol (3 mL). Stirred at RT overnight. Extracted into 200 mL dichloromethane and washed with brine (50 mL). Dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to yield title compound (1.00 g, 94% yield). ^1H-NMR ($CDCl_3$) δ (ppm): 8.81 (d, 2H), 7.62 (d, 2H), 3.68 (s, 3H), 2.82 (s, 3H).

Example 6

4-(4-Cyclopropyl-5-methylsulfanyl-4H-[1,2,4]triazol-3-yl)-pyridine

A solution of iodomethane (0.457 mL, 7.33 mmol) in ethanol (3 mL) was added to a solution of 4-cyclopropyl-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione (1 g, 4.58 mmol) in 1M sodium hydroxide (10 mL) at room temperature. After stirring overnight, the reaction mixture was extracted with dichloromethane and then the organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford the titled compound (729.1 mg, 69%, beige solid). ^1H NMR ($CDCl_3$) δ (ppm): 8.77 (d, 2H), 7.75 (m , 2H), 3.23 (m, 1H), 2.82 (s, 3H), 1.17 (m, 2H), 0.80 (m, 2H).

Example 7

4-(5-Methanesulfonyl-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine

To a solution of 4-(4-methyl-5-methylsulfanyl-4H-[1,2,4]triazol-3-yl)-pyridine (1000 mg, 4.85 mmol) in acetic acid, added a solution of $KMnO_4$ (1.15 g, 7.28 mmol) in H_20 (50 mL) drop-wise. Stirred at RT for 3 hours. Added sodium hydrogen sulfite until purple color was discharged. Extracted into chloroform (3 x 100 mL). Washed organic layer with

saturated sodium bicarbonate (50 mL). Dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to yield title compound (1.01 g, 87% yield). ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.89 (d, 2H), 7.64 (d, 2H), 4.05 (s, 3H), 3.64 (s, 3H).

Example 8

4-(4-Cyclopropyl-5-methanesulfonyl-4H-[1,2,4]triazol-3-yl)-pyridine

A solution of potassium permanganate (525 mg, 3.3 mmol) in water (22.0 mL) was added to a solution of 4-(4-cyclopropyl-5-methylsulfanyl-4H-[1,2,4]triazol-3-yl)-pyridine (514 mg, 2.2 mmol) in acetic acid (11 mL) drop-wise at room temperature. After stirring for 3 hours, sodium hydrogen sulfite was added until the purple color was discharged. The reaction mixture was extracted with chloroform and then the organic layer was washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated to afford the titled compound (546.7 mg, 94%, white solid). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.86 (d, 2H), 7.77 (d , 2H), 3.64 (m, 1H), 3.63 (s, 3H), 1.25 (m, 2H), 1.01 (m, 2H).

Example 9

Methyl [(4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)thio]acetate

1.75 g (9.15 mmol) 4-Methyl-5-pyridin-3-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione and 2.47 g (17.8 mmol) K_2CO_3 were dissolved, respectively suspended in MeCN (25 mL) and five drops of DMF were added, followed by 0.81 mL (9.18 mmol) methyl chloroacetate. The reaction was stirred under argon at r.t. o.n.. After filtration the filtrate was taken up in EA and washed with water. To the aq. layer was added brine and sodium bicarbonate, followed by extraction with DCM and EA. All organic layers were pooled and evaporated to dryness. Flash chromatography (DCM/MeOH=70/1 to 10/1) gave 2.19 g (91%) of the title compound.

^{1}H-NMR: 8.89 (d, 1H), 8.74 (dd, 1H), 8.01 (dd, 1H), 7.46 (m, 1H), 4.11 (s, 2H), 3.77 (s, 3H), 3.70 (s, 3H)

Example 10

[(4-Methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)thio]acetic acid

2.00 g (7.50 mmol) methyl [(4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)thio]acetate was dissolved in MeOH (30 mL). 0.45 g (8.0 mmol) Potassium hydroxide was added. After stirring at r.t. for 18 h the temperature was increased to 50°C. After further 3 h more potassium hydroxide was added (0.20 g) and stirring continued for additional 3 h. The mixture was cooled, diluted with aq. KOH and washed with EA. The aq. layer was acidified to pH 2 and evaporated to dryness, giving crude title product, which was used directly in the next step. ^{1}H-NMR(DMSO-d6): 8.98 (d, 1 H), 8.80 (dd, 1 H), 8.26 - 8.35 (m, 1 H), 7.73 (dd, 1 H), 4.07 (s, 2 H), 3.66 (s, 3 H).

Example 11

N'-(3-Chlorophenyl)-2-[(4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)thio]acetohydrazide

Crude [(4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)thio]acetic acid from the previous step was dissolved under argon in DMF/MeCN (20 mL/20mL), followed by addition of 1.04 g (7.81 mmol) HOBt, 1.40 g (7.30 mmol) EDCl, 2 mL (20.6 mmol) DEA and 0.85 g (7.86 mmol) 3-chlorophenylhydrazine. After stirring for 1.5 hours the volume was reduced *in vacuo* and diluted with water. Extraction with EA, followed by washing with Na_2CO_3, citric acid and finally brine gave after evaporation a crude which was purified over silica (DCM/MeOH=30/1) yielding 1.07 g (40%) of the title compound. ^{1}H-NMR (DMSO-D6): 8.89 - 8.93 (m, 1 H), 8.74 (dd, 1 H), 8.07 - 8.18 (m, 2 H), 7.60 (dd, 1 H), 7.09 (t, 1 H), 6.62 - 6.74 (m, 3 H), 4.03 (s, 2 H), 3.65 (s, 4 H).

Example 12

5-(1-Chloroethyl)-2-(3-chlorophenyl)-1,2-dihydro-3H-1,2,4-triazol-3-one

$SOCl_2$ (1 mL, 8.4 mmol) was added to a solution of 2-(3-chlorophenyl)-5-(1-hydroxyethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (500 mg, 2.1 mmol) in DCM (15 mL). After stirring for 3 h the solvent and excess $SOCl_2$ were removed *in-vacuo*. Flash chromatography (MeOH/DCM 1:30) gave the title compound in 500 mg yield. ^{1}H NMR: 1.9 (d, 3 H) 5.0 (q, 1 H) 7.2 (ddd, 1 H) 7.4 (t, 1 H) 7.9 (dt, 1 H) 8.0 (t, 1 H) 11.9 (s, 1 H)

Example 13

2-(3-chlorophenyl)-5-(1-hydroxyethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

Sodium borohydride (300 mg, 7.9 mmol) in water (70 mL) was added to a solution of 5-acetyl-2-(3-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (2 g, 8.4 mmol) in MeOH (40 mL). Acetic acid (2 mL) was added after stirring for 5 min. The MeOH was removed under reduced pressure. After 12 h at 7°C the title compound was filtered off as in 2 g yield. ^{1}H-NMR: 1.5 (d, 3 H) 4.7 (q, 1 H) 7.1 (d, 1 H) 7.3 (m, 1 H) 7.8 (d, 1 H) 7.9 (s, 1 H)

Example 14

5-acetyl-2-(3-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

Phosgene (3.5 mmol) in toluene (1.8 mL) was added dropwise to a mixture of N'-(3-chlorophenyl)-2-oxopropanimidohydrazide (500 mg, 2.7 mmol) and pyridine (560 µl,7.1 mmol) in toluene (5 mL). The mixture was stirred for 2 h at r.t. under nitrogen, followed by filtration and washing with toluene. The solid was taken up in DCM and washed with water and brine. The solution was dried and concentrated. Flash chromatography (MeOH/DCM 1:40) gave the title compound in 200 mg yield. LC-MS (M^+ -1) 236

Example 15

N'-(3-chlorophenyl)-2-oxopropanimidohydrazide

3-Chlorobenzenediazonium tetrafluoroborate (10 g, 44 mmol) in water (300 mL) was added to a mixture of 3-chloropentane-2,4-dione (6 g, 44 mmol) and potassium acetate (8 g, 88 mmol) in MeOH (500 mL) at 0° C. After stirring for 30 min a formed solid was filtered off and recrystallized from MeOH. The crystals were re-dissolved in MeOH (200 mL) and the solution was added to 7 M ammonia in MeOH (100 mL). After stirring for 1 h, water was added leading to a precipitate which was filtered off and dried, giving the title compound in 5.5 g yield. LC-MS (M^+ -1) 210

Example 16

Ethyl 1-(3-chlorophenyl)-1H-pyrazole-4-carboxylate

3-Chlorophenylhydrazine hydrochloride (4.6 g, 25.7 mmol) in EtOH (100 mL) was added at 0 °C to a stirred solution of ethyl 2-formyl-3-oxopropanoate (3.7 g, 25.7 mmol) [J.Heterocyclic Chem. 1993, 30, 865-872] in EtOH (80 mL). After addition was completed

the reaction was allowed to reach rt, followed by stirring o.n. The reaction mixture was concentrated and the residue was recrystallized from EtOH to give 4.2 g (65%) of the title compound. ^{1}H NMR: 1.29 (t, 3H) 4.25 (q, 2H) 7.25 (d, 1H) 7.34 (t, 1H) 7.51 (d, 1H) 7.68 (s, 1H) 8.01 (s, 1H) 8.37 (s, 1H)

Example 17

[1-(3-chlorophenyl)-1H-pyrazol-4-yl]methanol

A solution of ethyl 1-(3-chlorophenyl)-1H-pyrazole-4-carboxylate (4.2g, 16.8 mmol) in Et_2O (100 mL) was slowly added to a stirred solution of $LiAlH_4$ (1.65 g, 43 mmol) in Et_2O (80 mL) at rt under nitrogen. The mixture was allowed to reach rt and was stirred for additional 1.5 h, followed by quenching via sequential addition of H_2O (2.6 mL), THF (6 mL) and 15 % aq. NaOH (2.6 mL). The mixture was stirred for 20 min, dried with Na_2SO_4, filtered and evaporated to dryness to give 3.4 g (97%) of the title compound. ^{1}H NMR: 4.68 (s, 2H) 7.24 (m, 1H) 7.36 (t, 1H) 7.53 (m, 1H) 7.72 (m, 2H) 7.91 (s, 1H)

Example 18

1-(3-chlorophenyl)-1H-pyrazole-4-carbaldehyde

MnO_2 was added to a solution of [1-(3-chlorophenyl)-1H-pyrazol-4-yl]methanol (3.4 g) in DCM (60 mL) at rt. The mixture was stirred at 40 °C o.n. The mixture was filtered through celite and the celite was washed with DCM (100 mL). The filtrate was evaporated to dryness to give 2.5 g (76%) of the title compound.. ^{1}H NMR: 7.35 (d, 1H) 7.33 (t, 1H) 7.60 (d, 1H) 7.79 (t, 1H) 8.16 (s, 1H) 8.43 (s, 1H) 9.96 (s, 1H)

Example 19

1-[1-(3-chlorophenyl)-1H-pyrazol-4-yl]ethanol

A solution of 1-(3-chlorophenyl)-1H-pyrazole-4-carbaldehyde (2.5 g, 12 mmol) in Et_2O (100 mL) was added to MeMgCl in THF (11 mL, 3 M, 30 mmol) at 0 °C. The reaction was stirred at 0 °C for 15 min and at rt for 2 h. Sat. aq. NH_4Cl was added and the mixture was extracted with Et_2O. The organic phase was dried and concentrated to give 2.7 g (100 %) of the title compound. ^{1}H NMR: 1.50 (d, 3H) 4.92 (q, 1H) 7.18 (m, 1H) 7.30 (t, 1H) 7.49 (m, 1H) 7.63 (s, 1H) 7.66 (t, 1H) 7.81 (s, 1H)

Example 20

1-[2-(3-chlorophenyl)-2H-1,2,3-triazol-4-yl]ethanol

A solution of 2-(3-chlorophenyl)-2H-1,2,3-triazole-4-carbaldehyde (1.2 g, 5.8 mmol) [J.Med. Chem, 1978, 21, 1254-1260] in Et_2O (70 mL) was added to MeMgCl in THF (4.8 mL, 3 M, 14.4 mmol) at 0 °C. The reaction was stirred at 0 °C for 30 min and at rt for 1 h. Sat. aq. NH_4Cl was added and the mixture was extracted with EA. The organic phase was dried and concentrated to give 1.14 g (100%) of the title compound. ^1H NMR: 1.58 (d, 3H) 5.08 (q, 1H) 7.25 (m, 1H) 7.33 (t, 1H) 7.71 (s, 1H) 7.88 (m, 1H) 8.02 (t, 1H)

Example 21

4-(1-chloroethyl)-2-(3-chlorophenyl)-2H-1,2,3-triazole

2 drops of DMF were added to 1-[2-(3-chlorophenyl)-2H-1,2,3-triazol-4-yl]ethanol (190 mg, 0.85 mmol) in $SOCl_2$ (3 mL) and the reaction was heated at 70 °C for 2 h. The excess $SOCl_2$ was evaporated and the residue was dried *in vacuo* to give the title compound in 206 mg (100%) yield. ^1H NMR: 1.95 (d, 3H) 5.28 (q, 1H) 7.31 (m, 1H) 7.40 (t, 1H) 7.83 (s, 1H) 7.95 (m, 1H) 8.08 (t, 1H)

Example 22

1-(3-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid methyl ester

A solution of 3-chlorobenzenediazonium chloride was prepared from 3-chloroaniline (2.2 mL, 21 mmol) in 10 % HCl (35 mL) and sodium nitrite (1.73 g, 25 mmol) in water (8 mL) 0 °C. This solution was added drop-wise with stirring to a mixture of methyl isocyanate (1.8 mL, 20 mmol), sodium acetate (13.1 g, 160 mmol), methanol (80 mL) and water (24 mL) over a period of 30 minutes at 0-5 °C. Stirring was continued for 1 h at the same temperature; then, methanol was removed in vacuo and the resultant products were extracted with EtOAc (500 mL). The combined organics were washed successively with 1 N HCl (100 mL), saturated $NaHCO_3$ (100 mL), water (100 mL) and brine (50 mL), then dried (Na_2SO_4), filtered and concentrated. The crude solid was recrystallized from boiling benzene to give 1.54 g (32 %) of the title compound as a brown solid. ^1H NMR ($CDCl_3$) δ

(ppm): 8.66 (s, 1H), 7.84 (m, 1H), 7.66 (m, 1 H), 7.47 – 7.53 (m, 2H), 4.08 (s, 3H), 1.60 (s, 2H).

Example 23

[1-(3-Chloro-phenyl)-1H-[1,2,4]triazol-3-yl]-methanol

A mixture of lithium borohydride (94 mg, 4.3 mmol) in 2-propanol (17 mL) was treated with 1-(3-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid methyl ester (0.50 g, 2.1 mmol). The flask was closed, and the reaction stirred overnight at room temperature. Water (5 mL) was added to decompose excess hydride, and the reaction mixture was adsorbed onto silica gel. Chromatography (SPE, 60 - 100 % EtOAc in hexanes) gave 186 mg (42%) of the desired product as a white solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.55 (s 1H), 7.75 (t, 1H), 7.58 (dt, 1H), 7.47 (t, 1 H), 7.40 (dt, 1H), 4.88 (d, 2H), 2.41 (t, 1H).

Example 24

Methanesulfonic acid 1-(3-chloro-phenyl)-1H-[1,2,4]triazol-3-ylmethyl ester

[1-(3-Chloro-phenyl)-1H-[1,2,4]triazol-3-yl]-methanol (87 mg, 0.42 mmol) was suspended in CH_2Cl_2 (5 mL) and the suspension was cooled to 0 °C. To this was added methanesulfonyl chloride (0.050 mL, 0.65 mmol) and triethylamine (0.12 mL, 0.86 mol). This solution was stirred at 0 °C for 1 h. To the reaction mixture in an ice bath was added cold saturated $NaHCO_3$ solution (5 mL). The organic phase was washed with brine (5 mL) then dried (Na_2SO_4), filtered and concentrated under educed pressure to give 99 mg (78 %) of a yellow oil, which NMR showed to be a 1:2 mixture of the title compound and 3-Chloromethyl-1-(3-chloro-phenyl)-1H-[1,2,4]triazole. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.59 (s, 0.67 H), 8.55 (s, 0.33 H), 7.71 (t, 1 H), 7.58 (dt, 1H), 7.41 – 7.49 (m, 2H), 5.42 (s, 1.27 H), 4.73 (s, 0.79 H), 2.82 (s, 2.3 H).

Example 25

[1-(3-Chloro-phenyl)-1H-[1,2,3]triazol-4-yl]-methanol

1-Azido-3-chlorobenzene (0.56 g, 3.7 mmol) and propargyl alcohol (0.18 mL, 3.1 mmol) were dissolved in t-butanol/water 1:1 (12 mL). Sodium ascorbate (1 M solution, 0.6 mL, 0.6 mmol) and copper sulfate pentahydrate (15 mg, 0.06 mmol) were added, and the

mixture was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried (Na_2SO_4), and concentrated. Chromatography (SPE, 5 % MeOH in 1:1 EtOAc/CH_2Cl_2) gave 275 mg (42 %) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.00 (d, J = 0.5 Hz, 1H), 7.80 (apparent t, J = 2 Hz, 1H), 7.65 (dq, J = 8, 2 Hz, 1H), 7.45 – 7.49 (m, 2H), 4.92 (d, J = 7 Hz, 2H), 2.48 (t, J = 7 Hz, 1H).

Example 26

Methanesulfonic acid 1-(3-chloro-phenyl)-1H-[1,2,3]triazol-4-ylmethyl ester

Methanesulfonyl chloride (0.11 mL, 1.4 mmol) was added to a solution of [1-(3-chloro-phenyl)-1H-[1,2,3]triazol-4-yl]-methanol (0.20 g, 0.95 mmol) and triethylamine (0.27 mL, 1.9 mmol) in CH_2Cl_2 (10 mL) at 0 °C, and the mixture was stirred at 0 °C for 1.5 h. Cold $NaHCO_3$ (saturated solution, 5 mL) was added, then the organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated crude yellow oil was triturated with ether to give 0.17 g (63 %) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.18 (s, 1H), 7.82 (td, 1H), 7.67 (dt, 1H), 7.45 – 7.55 (m, 2H), 5.48 (d, 2H), 5.48 (d, 2H).

Example 27

3-(3-chlorophenyl)-5-{[(4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)thio]methyl}-1,3,4-oxadiazol-2(3H)-one

1.04 g (2.77 mmol) N'-(3-chlorophenyl)-2-[(4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)thio]acetohydrazide was suspended in THF (100 mL) and cooled on an ice-water bath. 0.45 mL (5.62 mmol) TEA and 0.51 mg (3.14 mmol) CDI were added and the reaction was stirred under Ar at r.t. for 15.5 hours. Since no conversion had taken place, dioxane (50 mL) was added giving a homogeneous reaction mixture which was heated to 68°C. To this, additional 0.45 mL (5.62 mmol) TEA and 0.51 mg (3.14 mmol) CDI were added and finally 1.5 mL (2.8 mmol) of 20% phosgene in toluene together with 0.45 mL (5.62 mmol) TEA , followed by stirring for 2 h. Additional same amounts of phosgene and TEA were added after this and stirring again for 30 minutes. The reaction mixture was reduced *in vacuo* to about 2/3 of original volume, poured on ice/brine and extracted with EA, followed by washing with Na_2CO_3. The aq. layers were re-extracted with EA and the

organics pooled, dried (Na_2SO_4) and evaporated to dryness. The crude was filtered over silica (DCM/MeOH=30/1) and purified over silica using DCM/MeOH = 30/1, giving crude product which was further purified over silica using a slow gradient DCM neat to DCM/MeOH=80/1 to 1/1 giving after evaporation and drying 593 mg (53%) of the title compound. ^{1}H NMR: 8.87 (s, 1 H), 8.72 (d, 1 H), 7.93 - 8.06 (m, 1 H), 7.77 (t, 1 H), 7.64 - 7.73 (m, 1 H), 7.44 (dd, 1 H), 7.30 (t, 1 H), 7.15 - 7.21 (m, 1 H), 4.45 (s, 2 H), 3.67 (s, 3 H)

Example 28

2-(3-chlorophenyl)-5-{1-[methyl(4-methyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl)amino]ethyl}-2,4-dihydro-3H-1,2,4-triazol-3-one

NaH (3 mg, 0.1 mmol) was added to a solution of methyl-(4-methyl-5-pyridin-4-yl-4H-[1,2,4]triazol-3-yl)-amine (16 mg, 0.09 mmol) in DMF(2 mL) under nitrogen. After stirring for 10 min a solution of 5-(1-chloroethyl)-2-(3-chlorophenyl)-1,2-dihydro-3H-1,2,4-triazol-3-one (20 mg, 0.08 mmol) in DMF (1 mL) was added. After stirring for 1 h, 10 mL sat. aq. ammonium chloride was added and the mixture was extracted with EA. The organic phase was dried and concentrated. Prep. HPLC gave the desired product in 9 mg yield. ^{1}H NMR: 1.6 (d, 3 H), 2.8 (s, 3 H), 3.6 (s, 3 H), 4.7 (q, 1 H), 7.2 (d, 1 H), 7.3 (t, 1 H), 7.6 (s, 2 H), 8.0 (d, 1 H), 8.0 (s, 1 H), 8.8 (s, 2 H), 11.4 (s, 1 H)

Example 29

4-(5-{1-[1-(3-chlorophenyl)-1H-pyrazol-4-yl]ethoxy}-4-methyl-4H-1,2,4-triazol-3-yl)pyridine

NaH (28 mg, 1.16 mmol) was added to a solution of 1-[1-(3-chlorophenyl)-1H-pyrazol-4-yl]ethanol (100 mg, 0.45 mmol) and 4-[4-methyl-5-(methylsulfonyl)-4H-1,2,4-triazol-3-yl]pyridine (101 mg, 0.45 mmol) in DMF (5 mL). The reaction was stirred at 60 °C o.n. Brine was added and the mixture was extracted with EA. The organic phase was dried and concentrated. The product was purified by flash column chromatography (DCM to DCM-MeOH 40:1) afforded 43 mg (25%) of the title compound. ^{1}H NMR: 1.79 (d, 3H), 3.42 (s, 3H), 5.61 (q, 1H), 7.21 (m, 1H), 7.32 (t, 1H), 7.52 (m, 3H), 7.67 (t, 1H), 7.73 (s, 1H), 7.93 (s, 1H), 8.73 (d, 2H)

Example 30

4-(5-{1-[2-(3-chlorophenyl)-2H-1,2,3-triazol-4-yl]ethoxy}-4-methyl-4H-1,2,4-triazol-3-yl)pyridine

Cs_2CO_3 (171 mg, 0.52 mmol) was added to a solution of 3-[4-methyl-5-(methylsulfonyl)-4H-1,2,4-triazol-3-yl]pyridine (80 mg, 0.35 mmol) and 1-[2-(3-chlorophenyl)-2H-1,2,3-triazol-4-yl]ethanol (80 mg, 0.35 mmol) in DMF (20 mL). The reaction was stirred at 60 °C for 40 h. Brine was added and the mixture was extracted with EA. The organic phase was dried and concentrated. The product was purified by flash column chromatography (DCM to DCM-MeOH 40:1) to afford 23 mg (17%) of the title compound. ^{1}H NMR: 1.95 (d, 3H), 3.57 (s, 3H), 6.40 (q, 1H), 7.32 (d, 1H), 7.39 (t, 1H), 7.60 (m, 2H), 7.95 (m, 2H), 8.09 (t, 1H), 8.74 (d, 2H)

Example 31

4-[5-({1-[2-(3-chlorophenyl)-2H-1,2,3-triazol-4-yl]ethyl}thio)-4-cyclopropyl-4H-1,2,4-triazol-3-yl]pyridine

Cs_2CO_3 (130 mg, 0.40 mmol) was added to a solution of 4-cyclopropyl-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione (85 mg, 0.39 mmol) and 4-(1-chloroethyl)-2-(3-chlorophenyl)-2H-1,2,3-triazole (95 mg, 0.39 mmol) in DMF (4 mL). The reaction was stirred at 60 °C for 24 h. Brine was added and the mixture was extracted with EA. The organic phase was dried and concentrated. The product was purified by flash column chromatography (DCM to DCM-MeOH 40:1) to afford 113 mg (68 %) of the title compound. ^{1}H NMR: 0.73 (m, 2H), 1.12 (m, 2H), 1.98 (d, 3H), 3.16 (m, 1H), 5.42 (q, 1H), 7.30 (m, 1H), 7.40 (t, 1H), 7.70 (dd, 2H), 7.86 (s, 1H), 7.94 (m, 1H), 8.07 (t, 1H), 8.75 (dd, 2H)

Example 32

4-{5-[1-(3-Chloro-phenyl)-1H-[1,2,4]triazol-3-ylmethylsulfanyl]-4-cyclopropyl-4H-[1,2,4]triazol-3-yl}-pyridine

A solution of methanesulfonic acid 1-(3-chloro-phenyl)-1H-[1,2,4]triazol-3-ylmethyl ester (28 mg, 0.09 mmol), potassium carbonate (38 mg, 0.27 mmol) and 4-cyclopropyl-5-pyridin-4-yl-2,4-dihydro-[1,2,4]triazole-3-thione (20 mg, 0.09 mmol) in acetonitrile (3 mL) was stirred at room temperature for 16 h. The reaction mixture was diluted with

EtOAc (15 mL), then washed with water (10 mL). The aqueous phase was re-extracted with CH_2Cl_2 (10 mL), and the combined organics were washed with brine (15 mL), dried (Na_2SO_4), filtered and concentrated onto silica gel. Flash chromatography (SPE, 2-5 % MeOH in 1:1 CH_2Cl_2/EtOAc) gave14 mg (38 %) of the title compound as a white solid. ^1H NMR ($CDCl_3$) δ (ppm): 8.78 (d, J = 6 Hz, 2 H), 8.53 (s, 1H), 7.73 – 7.78 (m, 3H), 7.57 (dt, J = 8, 2 Hz, 1 H), 7.46 (t, J = 8 Hz, 1 H), 7.39 (dt, J = 8, 2 Hz, 1 H), 4.82 (s, 2H), 3.29 (5, J = 4 Hz, 1H), 1.15 – 1.28 (m, 4H).

Example 33

4-{5-[1-(3-Chloro-phenyl)-1H-[1,2,4]triazol-3-ylmethoxy]-4-cyclopropyl-4H-[1,2,4]triazol-3-yl}-pyridine

Sodium hydride (60 % oil dispersion, 12 mg, 0.30 mmol) was added to a solution of [1-(3-chloro-phenyl)-1H-[1,2,4]triazol-3-yl]-methanol (47 mg, 0.22 mmol) in DMF (3 mL) under argon and the mixture was stirred for 45 minutes. 4-(5-Methanesulfonyl-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine (39 mg, 0.15 mmol) was added, and the mixture was heated to 80 °C and stirred for 40 h. The reaction mixture was extracted with EtOAc (50 mL) and CH_2Cl_2 (25 mL), and the combined organics were washed with water (3 x 20 mL) and brine (30 mL), then dried (Na_2SO_4), filtered and concentrated onto silica gel. Chromatography (SPE, 5 % MeOH in 1:1 CH_2Cl_2/ EtOAc) afforded 18 mg of the title compound as a white solid. ^1H NMR ($CDCl_3$) δ (ppm): 8.75 (d, 2H), 8.60 (d, 1H), 7.78 – 7.80 (m, 3H), 7.78 (m, 1H), 7.67 – 7.74 (m, 3H), 5.76 (d, 2H), 3.22 (m, 1H), 1.08 – 1.12 (m, 2H), 0.86 – 0.90 (m, 2H).

Example 34

4-{5-[1-(3-Chloro-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-4-methyl-4H-[1,2,4]triazol-3-yl}-pyridine

A mixture of methanesulfonic acid 1-(3-chloro-phenyl)-1H-[1,2,3]triazol-4-ylmethyl ester (40 mg, 0.14 mmol), potassium carbonate (58 mg, 0.42 mmol) and 4-methyl-5-pyridin-4-yl-2,4-dihydro-[1,2,4]triazole-3-thione (27 mg, 0.14 mmol) in acetonitrile (5 mL) was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc and washed with water, and the aqueous phase was re-extracted with CH_2Cl_2. The combined

organics were washed with water and brine, then dried (Na_2SO_4), filtered and concentrated onto silica gel. Chromatography (SPE, 5-15 % MeOH in 1:1 CH_2Cl_2/EtOAc) yielded 39 mg (73 %) of a white solid. ^1H NMR ($CDCl_3$) δ (ppm): 8.80 (dd, J = 5, 2 Hz, 2H), 8.26 (s, 1H), 7.78 (t, J = 2 Hz, 1H), 7.58 – 7.64 (m, 3H), 7.46 (t, J = 7 Hz, 1H), 7.42 (dt, J = 7, 2 Hz, 1H), 4.71 (s, 2H), 3.65 (s 3H).

Example 35

4-{5-[1-(3-Chloro-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-4-cyclopropyl-4H-[1,2,4]triazol-3-yl}-pyridine

A mixture of methanesulfonic acid 1-(3-chloro-phenyl)-1H-[1,2,3]triazol-4-ylmethyl ester (40 mg, 0.14 mmol), potassium carbonate (58 mg, 0.42 mmol) and 4-cyclopropyl-5-pyridin-4-yl-2,4-dihydro-[1,2,4]triazole-3-thione (31 mg, 0.14 mmol) in acetonitrile (5 mL) was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc and washed with water, and the aqueous phase was re-extracted with CH_2Cl_2. The combined organics were washed with water and brine, then dried (Na_2SO_4), filtered and concentrated onto silica gel. Chromatography (SPE, 5-15 % MeOH in 1:1 CH_2Cl_2/EtOAc) yielded 45 mg (79 %) of a white solid. ^1H NMR ($CDCl_3$) δ (ppm): 8.78 (dd, 2H), 8.32 (s, 1H), 7.79 (t, 1 H), 7.74 (dd, 2H), 7.63 (dt, 1H), 7.37 – 7.48 (m, 2H), 4.74 (s, 2H), 3.23 (m, 1H), 1.14 – 1.27 (m, 2H), 0.77 – 0.82 (m, 2H).

Example 36

4-{5-[1-(3-Chloro-phenyl)-1H-[1,2,3]triazol-4-ylmethoxy]-4-cyclopropyl-4H-[1,2,4]triazol-3-yl}-pyridine

Sodium hydride (60 % oil dispersion, 13 mg, 0.32 mmol) was added to a solution of [1-(3-chloro-phenyl)-1H-[1,2,3]triazol-4-yl]-methanol (50 mg, 0.24 mmol) in DMF (3 mL), and the mixture was stirred for 45 minutes at room temperature. 4-(4-Cyclopropyl-5-methanesulfonyl-4H-[1,2,4]triazol-3-yl)-pyridine (42 mg, 0.16 mmol) was added, and the mixture was heated to 80 °C in an oil bath and stirred for 40 h. The mixture was diluted with EtOAc (30 mL) and washed with water (2 x 15 mL), and the aqueous phases were combined and re-extracted with CH_2Cl_2 (10 mL). The combined organics were washed with brine (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated onto silica gel.

Chromatography (SPE, 3-30 % MeOH in 1:1 CH_2Cl_2/EtOAc) afforded 18 mg (19 %) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 9.75 (m, 2H), 8.44 (s, 1H), 7.83 (td, J = 2, 0.5 Hz, 1H), 7.76 (dd, J = 5, 2 Hz, 2H), 7.67 (dt, J = 7, 2 Hz, 1H), 7.42 – 7.51 (m, 2H), 5.77 (s, 2H), 3.16 (7, J = 4 Hz, 1H), 1.08 – 1.16 (m, 2H), 0.76 – 0.80 (m, 2H).

Example 37

(1*R*)-1-[2-(3-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]ethyl acetate and (1*S*)-1-[2-(3-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]ethanol

Vinyl acetate (350 µL, 3.8 mmol) was added to 1-[2-(3-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]ethanol (650 mg, 2.9 mmol) and Novozyme 435® (80 mg) in toluene (10 mL) and the mixture was stirred at r.t. under an argon-atmosphere for 24 h. The mixture was filtered through celite and the celite was washed with DCM. The combined filtrate was evaporated and the residue was purified by flash column chromatography (SiO_2, DCM to DCM-MeOH 40:1) to give 320 mg (45%) of (1*R*)-1-[2-(3-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]ethyl acetate. ^{1}H NMR: 1.70 (d, 3 H), 2.12 (s, 3 H), 6.13 (q, 1 H), 7.33 (m, 1 H), 7.41 (t, 1 H), 7.77 (s, 1 H), 7.97 (dd, 1 H), 8.10 (t, 1 H). (1*S*)-1-[2-(3-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]ethanol was also obtained, in 49 % yield. ^{1}H NMR: 1.65 (d, 3 H), 5.15 (q, 1 H), 7.30 (m, 1 H), 7.40 (t, 1 H), 7.78 (s, 1 H), 7.95 (m, 1 H), 8.10 (t, 1 H)

Example 38

(1*R*)-1-[2-(3-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]ethanol

Lithium hydroxide monohydrate (102 mg, 2.43 mmol) was added to (1*R*)-1-[2-(3-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]ethyl acetate (323 mg, 1.21) in THF/water 1:1 (10 mL). After 18 h stirring at r.t the volume of the mixture was reduced *in vacuo* to about ½, followed by dilution with brine and extraction with EtOAc, 270 mg (100%) of the title compound was obtained after evaporation and drying. ^{1}H NMR: 1.64 (d, 3 H), 5.13 (q, 1 H), 7.31 (m, 1 H), 7.39 (t, 1 H), 7.76 (s, 1 H), 7.94 (m, 1 H), 8.08 (t, 1 H)

Example 39

4-(5-{(1*R*)-[2-(3-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]ethoxy}-4-methyl-4*H*-1,2,4-triazol-3-yl)pyridine

Cs_2CO_3 (326 mg, 1.0 mmol) was added to a solution (1*R*)-1-[2-(3-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]ethanol (149 mg, 0.67 mmol) and 4-[4-methyl-5-(methylsulfonyl)-4H-1,2,4-triazol-3-yl]pyridine (149 mg, 0.66 mmol) in DMF (5 mL). The reaction was stirred at 60 °C for 48 h. Brine was added and the mixture was extracted 3 times with EtOAc. The organic phase was dried and concentrated. The product was purified by flash column chromatography (SiO_2, DCM to DCM-MeOH 40:1) to give 69 mg (27%) of the title compound. ^{1}H NMR: 1.95 (d, 3 H), 3.57 (s, 3 H), 6.40 (q, 1 H), 7.32 (m, 1 H), 7.40 (t, 1 H), 7.65 (d, 2 H), 7.97 (m, 2 H), 8.10 (t, 1 H), 8.76 (br. s., 2 H)

Pharmacology

The pharmacological properties of the compounds of the invention can be analyzed using standard assays for functional activity. Examples of glutamate receptor assays are well known in the art as described in for example Aramori *et al., Neuron* 8:757 (1992), Tanabe *et* al., *Neuron* 8:169 (1992), Miller *et al., J. Neuroscience* 15: 6103 (1995), Balazs, *et al., J. Neurochemistry* 69:151 (1997). The methodology described in these publications is incorporated herein by reference. Conveniently, the compounds of the invention can be studied by means of an assay that measures the mobilization of intracellular calcium, $[Ca^{2+}]_i$ in cells expressing mGluR5.

For FLIPR analysis, cells expressing human mGluR5d as described in WO97/05252 were seeded on collagen coated clear bottom 96-well plates with black sides and analysis of $[Ca^{2+}]_i$ mobilization was done 24 h after seeding.

FLIPR experiments were done using a laser setting of 0.800 W and a 0.4 second CCD camera shutter speed. Each FLIPR experiment was initiated with 160 µl of buffer present in each well of the cell plate. After each addition of the compound, the fluorescence signal was sampled 50 times at 1 second intervals followed by 3 samples at 5 second intervals. Responses were measured as the peak height of the response within the sample period. EC_{50} and IC_{50} determinations were made from data obtained from 8-point concentration response curves (CRC) performed in duplicate. Agonist CRC were generated by scaling all responses to the maximal response observed for the plate. Antagonist block of the agonist challenge was normalized to the average response of the agonist challenge in 14 control wells on the same plate.

We have validated a secondary functional assay for mGluR5d as described in WO97/05252 based on Inositol Phosphate (IP_3) turnover. IP_3 accumulation is measured as an index of receptor mediated phospholipase C turnover. GHEK cells stably expressing the human mGluR5d receptors were incubated with [3H] myo-inositol overnight, washed three times in HEPES buffered saline and pre-incubated for 10 min with 10 mM LiCl. Compounds (agonists) were added and incubated for 30 min at 37°C. Antagonist activity was determined by pre-incubating test compounds for 15 min, then incubating in the presence of glutamate (80μM) or DHPG (30 μM) for 30 min. Reactions were terminated by the addition of perchloric acid (5%). Samples were collected and neutralized, and inositol phosphates were separated using Gravity-Fed Ion-Exchange Columns.

A detailed protocol for testing the compounds of the invention is provided in the assay below.

Assay of Group I receptor antagonist activity

For FLIPR analysis, cells expressing human mGluR5d as described in WO97/05252 were seeded on collagen coated clear bottom 96-well plates with black sides and analysis of $[Ca^{2+}]_i$ mobilization was performed 24 h following seeding. Cell cultures in the 96-well plates were loaded with a 4 μM solution of acetoxymethyl ester form of the fluorescent calcium indicator fluo-3 (Molecular Probes, Eugene, Oregon) in 0.01% pluronic. All assays were performed in a buffer containing 127 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 0.7 mM NaH_2PO_4, 2 mM $CaCl_2$, 0.422 mg/ml $NaHCO_3$, 2.4 mg/ml HEPES, 1.8 mg/ml glucose and 1 mg/ml BSA Fraction IV (pH 7.4).

FLIPR experiments were done using a laser setting of 0.800 W and a 0.4 second CCD camera shutter speed with excitation and emission wavelengths of 488 nm and 562 nm, respectively. Each FLIPR experiment was initiated with 160 μl of buffer present in each well of the cell plate. A 40 μl addition from the antagonist plate was followed by a 50 μL addition from the agonist plate. After each addition the fluorescence signal was sampled 50 times at 1 second intervals followed by 3 samples at 5 second intervals. Responses were measured as the peak height of the response within the sample period.

EC_{50}/IC_{50} determinations were made from data obtained from 8 points concentration response curves (CRC) performed in duplicate. Agonist CRC were generated by scaling all responses to the maximal response observed for the plate. Antagonist block of the agonist

challenge was normalized to the average response of the agonist challenge in 14 control wells on the same plate.

Measurement of Inositol Phosphate Turnover in Intact Whole Cells

GHEK stably expressing the human mGluR5d receptor were seeded onto 24 well poly-L-lysine coated plates at 40 x 10^4 cells /well in media containing 1 μCi/well [3H] myo-inositol. Cells were incubated overnight (16 h), then washed three times and incubated for 1 h at 37°C in HEPES buffered saline (146 mM NaCl, 4.2 mM KCl, 0.5 mM $MgCl_2$, 0.1% glucose, 20 mM HEPES, pH 7.4) supplemented with 1 unit/ml glutamate pyruvate transaminase and 2 mM pyruvate. Cells were washed once in HEPES buffered saline and pre-incubated for 10 min in HEPES buffered saline containing 10 mM LiCl. Compounds (agonists) were added and incubated at 37°C for 30 min. Antagonist activity was determined by pre-incubating test compounds for 15 min, then incubating in the presence of glutamate (80 μM) or DHPG (30 μM) for 30 min. The reaction was terminated by the addition of 0.5 ml perchloric acid (5%) on ice, with incubation at 4°C for at least 30 min. Samples were collected in 15 ml Falcon tubes and inositol phosphates were separated using Dowex columns, as described below.

Assay For Inositol Phosphates Using Gravity-Fed Ion-Exchange Columns

Preparation of Ion- Exchange Columns

Ion-exchange resin (Dowex AG1-X8 formate form, 200-400 mesh, BIORAD) was washed three times with distilled water and stored at 4°C. 1.6 ml resin was added to each column, and washed with 3 ml 2.5 mM HEPES, 0.5 mM EDTA, pH 7.4.

a) Sample Treatment

Samples were collected in 15 ml Falcon tubes and neutralized with 0.375 M HEPES, 0.75 M KOH. 4 ml of HEPES / EDTA (2.5 / 0.5 mM, pH 7.4) were added to precipitate the potassium perchlorate. Supernatant was added to the prepared Dowex columns.

b) Inositol Phosphate Separation

Elute glycero phosphatidyl inositols with 8 ml 30 mM ammonium formate.

Elute total inositol phosphates with 8 ml 700 mM ammonium formate / 100 mM formic acid and collect eluate in scintillation vials. Count eluate mixed with 8 ml scintillant.

One aspect of the invention relates to a method for inhibiting activation of mGluR5, comprising treating a cell containing said receptor with an effective amount of the compound of formula I.

Screening for compounds active against tlesr

Adult Labrador retrievers of both genders, trained to stand in a Pavlov sling, are used. Mucosa-to-skin esophagostomies are formed and the dogs are allowed to recover completely before any experiments are done.

Motility measurement

In brief, after fasting for approximately 17 h with free supply of water, a multilumen sleeve/sidehole assembly (Dentsleeve, Adelaide, South Australia) is introduced through the esophagostomy to measure gastric, lower esophageal sphincter (LES) and esophageal pressures. The assembly is perfused with water using a low-compliance manometric perfusion pump (Dentsleeve, Adelaide, South Australia). An air-perfused tube is passed in the oral direction to measure swallows, and an antimony electrode monitored pH, 3 cm above the LES. All signals are amplified and acquired on a personal computer at 10 Hz.

When a baseline measurement free from fasting gastric/LES phase III motor activity has been obtained, placebo (0.9% NaCl) or test compound is administered intravenously (i.v., 0.5 ml/kg) in a foreleg vein. Ten min after i.v. administration, a nutrient meal (10% peptone, 5% D-glucose, 5% Intralipid, pH 3.0) is infused into the stomach through the central lumen of the assembly at 100 ml/min to a final volume of 30 ml/kg. The infusion of the nutrient meal is followed by air infusion at a rate of 500 ml/min until an intragastric pressure of 10±1 mmHg is obtained. The pressure is then maintained at this level throughout the experiment using the infusion pump for further air infusion or for venting air from the stomach. The experimental time from start of nutrient infusion to end of air insufflation is 45 min. The procedure has been validated as a reliable means of triggering TLESRs.

TLESRs is defined as a decrease in lower esophageal sphincter pressure (with reference to intragastric pressure) at a rate of >1 mmHg/s. The relaxation should not be preceded by a pharyngeal signal ≤2s before its onset in which case the relaxation is classified as swallow-induced. The pressure difference between the LES and the stomach should be less than 2 mmHg, and the duration of the complete relaxation longer than 1 s.

Abbreviations

BSA	Bovine Serum Albumin
CCD	Charge Coupled Device
CRC	Concentration Response Curve
DHPG	3,5-dihydroxyphenylglycine;
EDTA	Ethylene Diamine Tetraacetic Acid
FLIPR	Fluorometric Imaging Plate reader
GHEK	GLAST-containing Human Embrionic Kidney
GLAST	glutamate/aspartate transporter
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (buffer)
IP_3	inositol triphosphate

Results

Typical IC_{50} values as measured in the assays described above are 10 μM or less. In one aspect of the invention the IC_{50} is below 2 μM. In another aspect of the invention the IC_{50} is below 0.2 μM. In a further aspect of the invention the IC_{50} is below 0.05 μM.

Compound	FLIPR IC_{50}
4-(5-{1-[2-(3-chlorophenyl)-2H-1,2,3-triazol-4-yl]ethoxy}-4-methyl-4H-1,2,4-triazol-3-yl)pyridine	27 nM
4-[5-({[1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl]methyl}thio)-4-cyclopropyl-4H-1,2,4-triazol-3-yl]pyridine	265 nM